KYNURENINE 3-HYDROXYLASE INHIBITORS FOR THE TREATMENT OF DIABETES BY INCREASING THE NUMBER OF ISLETS OF LANGERHANS CELLS

The present invention relates to compounds with inhibitory activity on kynurenine 3-hydroxylase and in particular to their use as products for pharmaceutical use by increasing the number of islets of Langerhans cells in the case of patients in need thereof, especially for the prevention and treatment of diabetes and related its complications and/or related pathologies (obesity, hypertension, etc.).

Diabetes mellitus represents a very heterogeneous group of diseases all having a certain number of characteristics in common: elevation of glycaemia and increased long-term risk of developing cardiovascular complications.

In 1985, according to the criteria of the WHO, two major types of diabetes are distinguished: insulin-dependent diabetes (IDD), which involves the manifestation of immunological phenomena, and non-insulin-dependent diabetes (NIDD), which were previously known as type-1 and type-2 diabetes, respectively (World Health Organization, 1985). The diabetes is said to be insulin-dependent if its symptoms (thirst, polyuria, coma, etc.) are associated with hyperglycaemia and ketosis: the administration of insulin is then vital from the early stages of the disease. In the majority of other cases, even if persistence of the hyperglycaemia secondarily necessitates the administration of insulin, the diabetes is considered as non-insulin-dependent and is treated in general using oral antidiabetic agents. Non-insulin-dependent diabetes currently affects 110 million people worldwide. This number shows no sign of decreasing, since it is forecast that 216 million people will be affected by 2010.

Maintaining a sugar balance requires strict coordination between the organs (brain, liver, pancreas, muscles and adipose tissue mainly) involved in energy metabolism.

In non-insulin-dependent diabetes, the liver and the pancreas are the main participants. Specifically, it has been clearly demonstrated that excessive

production of glucose by the liver is responsible for fasted hyperglycaemia in diabetics (Consoli et *al.*, *Diabetes*, Vol. 38 (1989), 550-557). Similarly, impairment in pancreatic function (number of islets of Langerhans cells, secretion of insulin and glucagon in response to glucose) contributes to the development of postprandial hyperglycaemia (Polonsky et *al.*, *N. Engl. J. Med.*, **318** (1988), 1231-39).

Insulin-dependent diabetes is an autoimmune disease that destroys the beta cells of the pancreas. This disease involves genetic factors (genes of the HLA (human leukocyte antigen) system and of insulin itself) and also environmental factors of nutritional and/or viral origin.

In addition to the hyperglycaemia symptoms and the complications resulting therefrom, the two types of diabetes have in common a defect of pancreatic origin.

The pancreas is a mixed organ comprising exocrine tissue, the role of which is the synthesis and secretion of the enzymes required for digestion, and an endocrine tissue composed of several types of cells, the role of which is to synthesise and secrete the hormones involved in maintaining carbohydrate homeostasis. The endocrine cells are grouped together in the exocrine pancreas in the form of small structures of complex cellular organisation known as islets of Langerhans. These islets are composed of four major cell types:

beta cells, which secrete insulin

alpha cells, which secrete glucagon

delta cells, which secrete somatostatin

PP cells, which secrete pancreatic polypeptide.

The amount of circulating insulin is controlled by rapid changes in the amount of hormone released by individual beta cells as a function of the variations in plasmatic glucose. However, a longer-term regulation also exists, which makes it possible to adapt the production of insulin by means of changes in the total mass of beta cells. The pancreas is capable of adapting its mass of beta cells when the demand for insulin increases. The increase in this demand is observed in physiological and physiopathological situations in which there is a reduction in the biological efficacy of insulin (insulin resistance). Besides an anomaly of secretion of pancreatic hormones (glucagon and insulin), an insuffi-

ciency in the number of islets of Langerhans cells and more particularly of beta cells may also contribute towards the secretory deficit and thus towards the establishment of hyperglycaemia in the case of type I and II diabetics (Klöppel G. et al. Surv. Synth. Path. Res (1985), 4 : 110125). Several studies performed on animal models of diabetes show that the genetic terrain is an important parameter in the growth of beta cells (Andersson A., Diabetologia (1983); 25 : 269-272.; Swenne I. Diabetes, (1984), 32 : 14-19).

In the course of diabetes, three stages are distinguished in the evolution:

- not requiring insulin
- requiring insulin
- insulin required for survival.

Separation of the description of the types of diabetes and of their evolutive stages shows the importance of avoiding the assimilation of insulin-dependent diabetes and diabetes treated with insulin. However, for non-insulin-dependent diabetes, an early stage and a late stage are conventionally distinguished, relating to the duration and seriousness of the diabetic condition.

The main treatment for type I diabetes consists of the subcutaneous injection of insulin. The clinical manifestation of diabetes is always preceded by a longer or shorter asymptomatic period known as prediabetes, during which organs can, however, become affected long before the diabetes is diagnosed.

In 2002, the American Diabetes Association suggested a new definition of prediabetes, namely a condition characterised by blood glucose concentrations that are higher normal, but lower than those corresponding to the predefined criteria of diabetes. A normal glycaemic equilibrium is characterised by a fasting glycaemia of less than 1.10 g/l and a glycaemia after meals of less than 1.40 g/l. If the fasting glycaemia is 1.26 g/l or greater and/or increases to more than 2 g/l after meals, diabetes is diagnosed.

More specifically, the prediabetic condition corresponding to type I diabetes may be defined by the presence of immunological markers, such as those described by Buysschaert et al, Louvain Méd. 119, S251-S258, 2000, especially including the anti-islet (ICA), anti-glutamic acid decarboxylase (GAD), anti-tyro-

sine phosphatase (IA-2) and anti-(pro)insulin (AIA) auto-antibodies, or the anti-carboxypeptidase H, anti-64kD and anti-heat shock protein antibodies.

The type II prediabetic condition is characterised mainly by a disappearance of the early peak of insulin secretion, the consequence of which is glucose intolerance (also known as IGT, for "impaired glucose tolerance") or impaired fasting glycaemia (also known as IFG, for "impaired fasting glucose").

No medicament exists for effectively preventing diabetes. It is thus desirable to provide novel routes for the prevention and/or treatment of prediabetes or diabetes. The main treatment of type I diabetes consists of the subcutaneous injection of insulin. For type II diabetes, it is legitimate to propose a medicinal treatment when the level of glycated haemoglobin (A1c) remains higher than 7% after 3 to 6 months of the only hygieno-dietetic measurements. It is necessary to do this if the A1c remains higher than 8% (Nathan, N.E.J.M., (2002), 17 : 1342-1349). Type II diabetes is generally treated using oral active medicaments. Although many oral antidiabetic agents are nowadays available, none of them makes it possible to achieve a normalisation of the glycaemic control parameters. The diabetic complications associated with hyperglycaemia inevitably appear. The main weakness of these medicaments is that they address only one defect at a time, either insulin resistance (thiazolidinediones or biguanides) or insulin secretion (sulfonylureas, glinides, etc.). Furthermore, no medicament capable of increasing the number and functionality of the islets of Langerhans cells is available at the present time. Finally, some of them have non-negligible adverse effects. Sulfonylureas in particular present a major risk of hypoglycaemia, which demands that the dosage of these medicaments be scrupulously defined and complied with from patient to patient. Simultaneous correction of the two defects mentioned above without risks of associated hypoglycaemia would constitute a fundamental breakthrough in the treatment of type II diabetes and its complications. The prevention of the associated cardiovascular risk, which represents one of the major complications, would also be of important benefit to diabetic patients.

With the pancreatic and hepatic function as the central focus in diabetic pathology in the present invention, the Inventors focused on a metabolic pathway, namely the metabolism of tryptophan. Tryptophan is an amino acid whose

involvement in controlling carbohydrate metabolism has previously been reported (Tsiolakis D. and V. Marks, *Horm. Metabol. Res.*, **16** (1964), 226-229). Its complex metabolisation via kynurenine leads to the production of NAD+. Some of the intermediate metabolites have also been described as possibly being involved in glycaemia control (Connick J. and Stone, *Medical hypothesis*, **18** (1985), 371-376) and in particular in the mechanisms for controlling the production of glucose by the liver ("*Effect of tryptophan and its metabolites on GNG in mammalian tissues*", Pogson et *al.*, 1975) and/or in insulin secretion and synthesis (Noto Y. and Okamoto, *Acta Diabet. Lat.*, **15** (1978), 273-282; Rogers and Evangelista, *Proc. Soc. Exp.*, **178** (1985), 275-278). Among the active metabolites of this pathway are tryptophan itself, kynurenine and kynurenic acid. The concentration of these metabolites is controlled by three enzymes: kynurenine 3-hydroxylase, kynureninase and kynurenine aminotransferase. Kynurenine aminotransferase has also been suspected of being involved in the hypertension physiopathology of SHR rats (Spontaneously Hypertensive Rat; Kwok et *al.*, JBC, 35779-35782, September 2002) which are otherwise insulin-resistant. Despite that, the joint action of these metabolites on glucose production by the liver and on insulin secretion in response to glucose has not been demonstrated in the prior art. In particular, it has not been demonstrated that some of these metabolites can restore a physiological response to glucose, the secretion of the pancreatic hormones (insulin and glucagon), in animals rendered diabetic by injection of streptozotocin, which would thus make it possible to correct the insulin secretion defect without giving rise to any risk of hypoglycaemia.

It is well described in the prior art that certain metabolites of the kynurenine pathway, such as quinolinic acid and kynurenic acid, act as neurotoxic agents and neuroprotective agents, respectively, on the nervous system. These effects are linked to their capacity to modulate glutamate receptors and/or nicotinic receptors (Schwarcz R. and Pellicciardi R., *JPET* **303** (2002), 1-10; Stone and Darlington, *Nature Reviews*, **1** (2002), 609-620). The presence of glutamate receptors in the pancreas is described in the prior art, as is their involvement in pancreatic hormone secretion (Weaver C. et *al.*, *J. Biol. Chem.*, **271**

(1996), 12977-12984), but it has not been demonstrated that these glutamate receptors are controlled by the kynurenine metabolites in this organ.

The research conducted with the aim of meeting the objectives of the present invention has made it possible to demonstrate, surprisingly, that the modulation of tryptophan metabolism in the kynurenine pathway via the pancreatic inhibition of kynurenine 3-hydroxylase allows an increase in the number of islets of Langerhans cells and thus plays an important role especially in the prevention and treatment of diabetic diseases, its complications and/or its related pathologies (obesity, hypertension, etc.).

One of the objectives of the present invention consequently consists in providing novel therapeutic means which have curative and/or preventive activity for the prevention of diabetes, its complications and/or its related pathologies, by increasing the number of islets of Langerhans cells, and which are free of the risk of hypoglycaemia.

The present invention also proposes, as another objective, a process for the treatment of diabetes that makes it possible to avoid the side effects and especially hypoglycaemia, the said process using therapeutic means whose mechanism of action for this type of pathology is not described or suggested in the prior art.

Certain compounds are known (see patents US 6 048 896 and US 6 323 240), which have inhibitory activity on the kynurenine 3-hydroxylase and which are useful in the treatment of neurodegenerative diseases, including diseases of the central nervous system, sclerosis and glaucoma-related retinopathy. Such compounds were already known as having analgesic and anti-inflammatory properties.

The research conducted with the aim of meeting the objectives of the present invention has made it possible to demonstrate, surprisingly, that the inhibition of kynurenine 3-hydroxylase plays an important role in the prevention and

treatment of diabetic diseases, in particular non-insulin-dependent diabetes, its complications and/or its related pathologies.

It has thus been discovered that compounds with inhibitory activity on kynurenine 3-hydroxylase increase the number of islets of Langerhans cells and are especially useful for the prevention and treatment of diabetes, its complications and/or its related pathologies.

The present inventors have now discovered, entirely unexpectedly, that kynurenine 3-hydroxylase inhibitors show activity towards pancreatic beta cells.

Specifically, according to the present invention, the kynurenine 3-hydroxylase inhibitors increase the number of islets of Langerhans cells and in particular the beta cells.

The use of kynurenine 3-hydroxylase inhibitors should thus make it possible to compensate for the reduction in the number of pancreatic islets of Langerhans cells in the course of the diabetic condition, in addition to their effect on the function of these cells.

According to the invention, kynurenine 3-hydroxylase inhibitors thus make it possible to prevent diabetes and its effects.

According to the invention, kynurenine 3-hydroxylase inhibitors thus make it possible to specifically target the treatment of hyperglycaemia as a function of the type of diabetes, its degree of progress and/or the population concerned.

Also, the use of kynurenine 3-hydroxylase inhibitors makes it possible to act selectively on the increase in the number of islets of Langerhans cells. This therefore makes it possible to selectively target patients with an anomaly of insulin secretion of the islets of Langerhans cells in response to glucose and/or an impairment in their number.

Specifically, the use of kynurenine 3-hydroxylase inhibitors makes it possible to treat and/or prevent insulin-dependent diabetes, by increasing the mass of insulin-secreting islets of Langerhans cells.

More particularly, kynurenine 3-hydroxylase inhibitors make it possible to prevent insulin-dependent diabetes by increasing the number of insulin-secreting islets of Langerhans cells before the disease has been declared, more particularly during prediabetes.

Also, the use of kynurenine 3-hydroxylase inhibitors makes it possible to treat and/or prevent early non-insulin-dependent diabetes, by increasing the number of functional cells. This is particularly advantageous insofar as this use makes it possible to avoid increasing the number of non-functional beta cells and reducing the mass of beta cells, respectively, above or below the normal value, which thus makes it possible to advantageously avoid the appearance of diabetes, its symptoms and/or its complications.

Also, the use of kynurenine 3-hydroxylase inhibitors makes it possible to treat and/or prevent non-insulin-dependent diabetes at an advanced stage, known as a late stage, by replacing the non-functional beta cells with functional beta cells.

Also, the use of kynurenine 3-hydroxylase inhibitors makes it possible to treat and/or prevent late non-insulin-dependent diabetes by regenerating the number of beta cells, following the failure and/or a reduction in the number of the beta cells.

According to the invention, the kynurenine 3-hydroxylase inhibitors may be administered orally, in monotherapy, to prevent and/or treat non-insulin-dependent diabetes.

According to the invention, the kynurenine 3-hydroxylase inhibitors can be used in vitro for the treatment of pancreatic stem cells; the said treated cells may be transplanted into a patient to prevent and/or treat non-insulin-dependent diabetes.

According to the invention, the kynurenine 3-hydroxylase inhibitors can be used in vitro for the treatment of pancreatic stem cells; the said treated cells may be transplanted into a patient to prevent and/or treat insulin-dependent diabetes.

According to the invention, the kynurenine 3-hydroxylase inhibitors may be administered in combination with one or more agents for reducing the body's immune response, to prevent and/or treat insulin-dependent diabetes.

According to a first subject, the present invention thus relates to the use of a kynurenine 3-hydroxylase inhibitor for the manufacture of a medicament for increasing the number of islets of Langerhans cells.

According to a second subject, the present invention relates to the use of a kynurenine 3-hydroxylase inhibitor for the manufacture of a medicament for the the treatment and/or prevention of insulin-dependent diabetes.

According to another subject, the present invention relates to the use of a kynurenine 3-hydroxylase inhibitor for the manufacture of a medicament for the prevention and/or treatment of insulin-dependent prediabetes.

According to another subject, the present invention relates to the use of a kynurenine 3-hydroxylase inhibitor for the manufacture of a medicament for the prevention of non-insulin-dependent diabetes.

According to another subject, the present invention relates to the use of a kynurenine 3-hydroxylase inhibitor for the manufacture of a medicament for the treatment of early non-insulin-dependent diabetes.

According to another subject, the present invention relates to the use of a kynurenine 3-hydroxylase inhibitor for the manufacture of a medicament for the treatment of late non-insulin-dependent diabetes.

According to another subject, the present invention relates to pharmaceutical compositions comprising a kynurenine 3-hydroxylase inhibitor in combination with one or more immunosuppressants.

According to another subject, the present invention also relates to the use of a kynurenine 3-hydroxylase inhibitor in combination with one or more immuno-

suppressants, for the manufacture of a medicament for the prevention and/or treatment of insulin-dependent diabetes.

According to a preferred aspect, the present invention relates to any of the uses mentioned above in the case of a patient with an impairment in the number of islets of Langerhans cells. Preferably, the impairment in the number of islets of Langerhans cells represents a decrease of at least 40% in the number of cells, more preferably a decrease of between 50% and 90%, and even more preferably between 60% and 85%.

According to a preferred aspect, the present invention relates to any of the uses mentioned above in the case of a patient presenting anti-islets of Langerhans cells immunological markers.

According to a preferred aspect, the present invention relates to any of the uses mentioned above in the case of a patient presenting any diabetic risk factor.

According to a preferred aspect, the present invention relates to any of the uses mentioned above in the case of a patient with insulin resistance.

According to a preferred aspect, the present invention relates to any of the uses mentioned above in the case of a patient presenting markers, such as glycated haemoglobin at concentrations higher than 7%.

According to a preferred aspect, the present invention relates to any of the uses mentioned above in the case of a patient whose islets of Langerhans cells show an anomaly of insulin secretion in response to glucose.

According to a preferred aspect, the present invention relates to any of the uses mentioned above in the case of a patient with related hyperglycaemia and obesity.

According to another aspect, the present invention relates to any of the uses mentioned above, comprising the in vitro treatment of isolated islets of Langerhans cells with a kynurenine 3-hydroxylase inhibitor.

According to another subject, the present invention also relates to the method for the in vitro treatment of isolated islets of Langerhans cells with a kynurenine 3-hydroxylase inhibitor.

The culturing and transplantation of the said islets of Langerhans cells may especially be performed by application or adaptation of the methods described by Docherty et al., Current Opinion in Pharmacology 2001, 1 :641-650.

According to the present invention, the term "prediabetes" means a condition characterised by one or more of the following factors: the presence of anti-islets of Langerhans cells immunological markers, an impairment in the number of islets of Langerhans cells, suppression of the early peak of insulin secretion, glucose intolerance, an impairment in fasting glycaemia and/or any diabetic risk factor.

According to the invention, the expression "impairment in fasting glycaemia and/or glucose intolerance" means a fasting glycaemia of between 1.10 g/l and 1.26 g/l and a glycaemia after meals of between 1.40 g/l and 2 g/l after meals.

According to the invention, the expression "anti-islets of Langerhans cells immunological markers" means any immunological marker indicating the existence of an autoimmune response of the body directed against the antigenic markers of the body's islets of Langerhans cells. These markers include auto-antibodies, such as those described by Buysschaert et al., Louvain Méd. 119, S251-S258, 2000. These antibodies are chosen from the anti-islet (ICA), anti-glutamic acid decarboxylase (GAD), anti-tyrosine phosphatase (IA-2) and anti-(pro)insulin (AIA) auto-antibodies, or the anti-carboxypeptidase H, anti-64kD and anti-heat shock protein antibodies.

According to the invention, the expression "impairment in the number of islets of Langerhans cells" means a decrease of at least 40% in the number of cells. Preferably, the impairment in the number of islets of Langerhans cells represents a decrease of at least 40% in the number of cells, more preferably a decrease of between 50% and 90% and even more preferably between 60% and 85%.

According to the invention, the expression "anomaly of insulin secretion in response to glucose" means any impairment in the normal capacity of the islets of Langerhans cells to secrete insulin in response to glucose.

According to the invention, the expression "diabetic risk factor" means any complaint directly or indirectly associated with the appearance of diabetes. These especially comprise familial history, gestational diabetes, excess weight, obesity, insufficient physical exercise, high blood pressure, a high level of triglycerides, inflammation, hyperlipidaemia, etc.

According to the invention, the term "immunosuppressant" means any physical agent (for example x-rays) chemical agent (for example azathioprine or mercaptopurine) or biological agent (for example anti-lymphocyte serum) for reducing or inhibiting the stimulation of an immune response of the body with an antigen.

According to the invention, the term "islets of Langerhans cells" means the alpha, beta, delta and PP cells mentioned above; more preferably, the islets of Langerhans cells represent the beta cells.

It has especially been discovered that the compounds corresponding to the general formula (I) or to the general formula (II) described hereinbelow generally have inhibitory activity on kynurenine 3-hydroxylase. Among the compounds described in formulae (I) and (II), some families of compounds are known to have activity that is useful in the treatment of diabetes, and especially the fami-

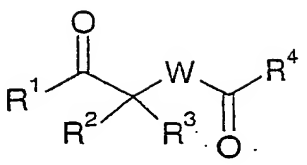
lies of compounds corresponding to patent application WO-A-98/07681 and the families corresponding to patent application EP-A-0 885 869. The compounds with substantial activity on kynurenine 3-hydroxylase are especially preferred. The term "substantial activity" means any inhibitory activity on the enzyme by the in vitro test process defined below, thus making it possible to obtain an effective therapeutic action on the enzyme. In particular, an enzymatic activity of less than or equal to 70%, advantageously less than or equal to 50% and even more preferably less than or equal to 30% relative to the control, is preferred.

It has thus been discovered that, within these families of compounds, it is possible to use compounds that are characterised by inhibitory activity on kynurenine 3-hydroxylase to obtain an improved treatment or improved medicaments, or for a different purpose, to increase the mass of beta cells and especially to prevent or treat diabetes, and also the complications of this diabetes, via a novel route that offers unexpected advantages. They also make it possible to improve the prevention and treatment of diabetes, especially of non-insulin-dependent diabetes, by administration of a therapeutically effective amount to patients in need of inhibition of kynurenine 3-hydroxylase.

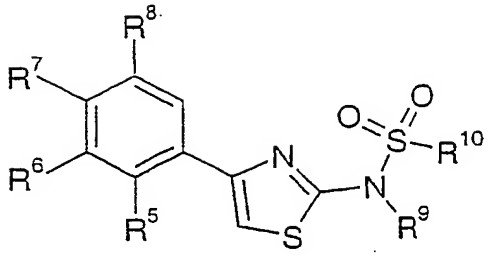
In particular, the compounds of family Ih are found to be noteworthy kynurenine 3-hydroxylase inhibitors and agents for increasing the mass of beta cells, especially antidiabetic agents.

Confirmation of the existence of inhibitory activity on kynurenine 3-hydroxylase may be made by any known means and especially, in a particularly simple manner, by subjecting the compound to an *in vitro* test that will be defined hereinbelow.

More specifically, the compounds with inhibitory activity on kynurenine 3-hydroxylase belong to the general formula (I) or to the general formula (II) below:



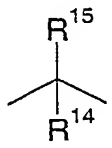
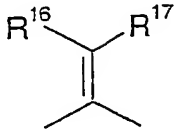
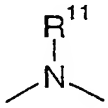
(I)



(II)

in which:

- W represents a divalent radical chosen from the following radicals:

 ;  ;  and  ;

- R^1 represents a radical chosen from linear or branched alkyl containing from 1 to 14 carbon atoms and optionally substituted, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, a heterocyclic radical, an aryl radical and a heteroaryl radical;
- R^2 is chosen from hydrogen, a halogen atom, hydroxyl, thiol, carboxyl, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylcarbonyl, alkoxycarbonyl, aryl, heteroaryl, cycloalkyl and a heterocyclic radical;
- R^3 is chosen from hydrogen, a halogen atom, hydroxyl, thiol, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, aryl, heteroaryl, cycloalkyl and a heterocyclic radical;
- R^2 and R^3 together also possibly forming a group $=CR^{16}R^{17}$; or alternatively together forming, with the carbon atom that bears them, a cycloalkyl radical or a heterocyclic radical;
- R^4 is chosen from hydroxyl, alkoxy, alkenyloxy, alkynyloxy, aryloxy, heteroaryloxy, $-N(R^{12}R^{12'})$, $-N(R^{12})OR^{13}$, linear or branched alkyl containing from 1 to 14 carbon atoms and optionally substituted, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl and a heterocyclic radical;
- R^5, R^6, R^7 and R^8, which may be identical or different, are chosen, independently of each other, from hydrogen, a halogen atom, and a nitro, cyano, hydroxyl, trifluoromethyl, alkyl, alkoxy, cycloalkyl or aryl radical;

- the radicals R^5 and R^6, on the one hand, or R^6 and R^7, on the other hand, may also form, together with the carbon atoms to which they are attached, a benzene ring optionally substituted by one or more groups, which may be identical or different, chosen from a halogen atom, a trifluoromethyl, cyano or nitro radical, an alkyl radical and an alkoxy radical;
- R^9 represents hydrogen or an alkyl radical;
- R^{10} is chosen from an alkyl, an aryl and a heteroaryl radical;
- R^{12} and $R^{12'}$, which may be identical or different, are chosen, independently of each other, from hydrogen and an alkyl, alkenyl, alkynyl, alkylcarbonyl, aryl or heteroaryl radical; or alternatively R^{12} and $R^{12'}$ may form, together with the nitrogen atom to which they are attached, a monocyclic or bicyclic heterocyclic group containing a total of 5 to 10 atoms, among which 1, 2, 3 or 4 are chosen, independently of each other, from nitrogen, oxygen and sulfur, the said heterocyclic radical also optionally comprising 1, 2, 3 or 4 double bonds and optionally being substituted by one or more chemical groups, which may be identical or different, chosen from hydroxyl, halogen atom, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, aryl, heteroaryl, heterocyclic radical and trifluoromethyl;
- R^{13} is chosen from hydrogen and an alkyl, alkenyl, alkynyl, aryl, heteroaryl, $-N(R^{12}R^{12'})$ or $-N(R^{12})OR^{13}$ radical;
- R^{14} is chosen from hydrogen, a halogen atom, hydroxyl, thiol, carboxyl, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylcarbonyl, alkoxycarbonyl, aryl, arylalkyl, heteroaryl, cycloalkyl and a heterocyclic radical;

R^{14} may also form a bond with R^2, thus forming a double bond between the carbon atoms respectively bearing the substituents R^{14} and R^2; or alternatively R^{14} forms, with R^2 and with the carbon atoms that bear them, a ring containing a total of 3, 4, 5, 6 or 7 carbon atoms, among which 1, 2 or 3 may be replaced with an atom chosen from nitrogen, oxygen and sulfur, the said ring possibly comprising one or more unsaturations in the form of (a) double bond(s), and being optionally substituted by one or more radicals, which may be identical or different, chosen from oxo, alkoxy, alkoxycarbonyl and alkylcarbonyloxy;

- R^{15} is chosen from hydrogen, a halogen atom, hydroxyl, thiol, carboxyl, alkyl, alkenyl, alkynyl, alkylcarbonyl, alkoxycarbonyl, alkoxy, alkenyloxy, alkynyloxy, aryloxy, cycloalkyloxy, heteroaryloxy, heterocyclyloxy, alkylthio, alkenylthio, alkynylthio, arylthio, cycloalkylthio, heteroarylthio, heterocyclylthio, aryl, heteroaryl, cycloalkyl and a heterocyclic radical;
- R^{14} and R^{15} also possibly forming, together with the carbon atom that bears them, a cycloalkyl radical or a heterocyclic radical;
- R^{16} and R^{17}, which may be identical or different, are chosen, independently of each other, from hydrogen, a halogen atom, an alkyl, aryl, heteroaryl or cycloalkyl radical and a heterocyclic radical; or alternatively
- R^{16} and R^{17} form, together with the carbon atom that bears them, a cycloalkyl radical or a heterocyclic radical; and
- R^{11} is chosen from hydrogen and an alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl or cycloalkylalkyl radical, and any protecting group for an amine function;

and also the possible geometrical and/or optical isomers thereof, and possible tautomeric forms thereof;

the solvates and hydrates of these compounds;

and also the possible salts thereof with a pharmaceutically acceptable acid or base, or alternatively the pharmaceutically acceptable prodrugs of these compounds.

The following definitions specify the natures of the various groups and radicals defined above. Unless otherwise indicated, these definitions apply for all the terms of the present invention thus explained.

The term "halogen atom" denotes a fluorine, chlorine, bromine or iodine atom.

The term "alkyl" denotes a linear or branched alkyl radical containing from 1 to 6 carbon atoms, optionally substituted by one or more chemical groups chosen from hydroxyl, carboxyl, cyano, nitro, $-N(R^{12}R^{12'})$, $-N(R^{12})OR^{13}$, aryl, heteroaryl,

cycloalkyl, heterocyclic radical, alkyl, alkenyl, alkynyl, alkoxy, alkylcarbonyl, alkoxycarbonyl, halogen atom, trifluoromethyl, thiol, $-SR^{13'}$, $-S(O)R^{13'}$ and $-S(O_2)R^{13'}$, with $R^{13'}$ having the same definition as R^{13}, with the exception of hydrogen. The possible substituents on the alkyl radical containing from 1 to 14 carbon atoms may be identical to those described above.

The term "alkenyl" denotes an alkenyl radical containing one or more double bonds; the said radical, which is linear or branched, and which contains from 2 to 6 carbon atoms, is optionally substituted by one or more chemical groups chosen from hydroxyl, carboxyl, cyano, nitro, $-N(R^{12}R^{12'})$, $-N(R^{12})OR^{13}$, aryl, heteroaryl, cycloalkyl, heterocyclic radical, alkyl, alkenyl, alkynyl, alkoxy, alkylcarbonyl, alkoxycarbonyl, halogen atom, trifluoromethyl, thiol, $-SR^{13'}$, $-S(O)R^{13'}$ and $-S(O_2)R^{13'}$, with $R^{13'}$ having the same definition as R^{13}, with the exception of hydrogen.

The term "alkynyl" denotes an alkynyl radical containing one or more triple bonds; the said radical, which is linear or branched, and which contains from 2 to 6 carbon atoms, is optionally substituted by one or more chemical groups chosen from hydroxyl, carboxyl, cyano, nitro, $-N(R^{12}R^{12'})$, $-N(R^{12})OR^{13}$, aryl, heteroaryl, cycloalkyl, heterocyclic radical, alkyl, alkenyl, alkynyl, alkoxy, alkylcarbonyl, alkoxycarbonyl, halogen atom, trifluoromethyl, thiol, $-SR^{13'}$, $-S(O)R^{13'}$ and $-S(O_2)R^{13'}$, with $R^{13'}$ having the same definition as R^{13}, with the exception of hydrogen.

The term "alkoxy" should be understood as being "alkyl" + "oxy", in which the term "alkyl" is as defined above. The substituents of the alkoxy radical are identical to those defined for the alkyl radical.

The term "cycloalkyl" denotes a bridged or non-bridged monocyclic, bicyclic or tricyclic cycloalkyl radical containing from 3 to 13 carbon atoms, optionally substituted by one or more chemical groups, which may be identical or different, chosen from hydroxyl, carboxyl, cyano, nitro, $-N(R^{12}R^{12'})$, $-N(R^{12})OR^{13}$, aryl, heteroaryl, cycloalkyl, heterocyclic radical, alkyl, alkenyl, alkynyl, alkoxy, alkylcarbonyl, alkoxycarbonyl, halogen atom, trifluoromethyl, thiol, $-SR^{13'}$, $-S(O)R^{13'}$ and $-S(O_2)R^{13'}$, with $R^{13'}$ having the same definition as R^{13}, with the exception of hydrogen.

The term "cycloalkenyl" denotes a cycloalkyl radical as defined above comprising at least one double bond.

The term "heterocyclic radical" or "heterocyclyl" denotes a monocyclic or bicyclic radical containing a total of 5 to 10 atoms, among which 1, 2, 3 or 4 are chosen, independently of each other, from nitrogen, oxygen and sulfur, the said heterocyclic radical also optionally comprising 1, 2, 3 or 4 double bonds and being optionally substituted by one or more chemical groups, which may be identical or different, chosen from hydroxyl, carboxyl, cyano, nitro, $-N(R^{12}R^{12'})$, $-N(R^{12})OR^{13}$, aryl, heteroaryl, cycloalkyl, heterocyclic radical, alkyl, alkenyl, alkynyl, alkoxy, alkylcarbonyl, alkoxycarbonyl, halogen atom, trifluoromethyl, thiol, $-SR^{13'}$, $-S(O)R^{13'}$ and $-S(O_2)R^{13'}$, with $R^{13'}$ having the same definition as R^{13}, with the exception of hydrogen.

The term "aryl" denotes a monocyclic, bicyclic or tricyclic aryl radical containing from 6 to 14 carbon atoms, optionally substituted by one or more chemical groups, which may be identical or different, chosen from hydroxyl, carboxyl, cyano, nitro, $-N(R^{12}R^{12'})$, $-N(R^{12})OR^{13}$, aryl, heteroaryl, cycloalkyl, heterocyclic radical, alkyl, alkenyl, alkynyl, alkoxy, alkylcarbonyl, alkoxycarbonyl, halogen atom, trifluoromethyl, thiol, $-SR^{13'}$, $-S(O)R^{13'}$ and $-S(O_2)R^{13'}$, with $R^{13'}$ having the same definition as R^{13}, with the exception of hydrogen.

The term "heteroaryl" denotes a monocyclic or bicyclic heteroaryl radical containing a total of 5 to 10 atoms, among which 1, 2, 3 or 4 are chosen, independently of each other, from nitrogen, oxygen and sulfur, the said heteroaryl radical being optionally substituted by one or more chemical groups, which may be identical or different, chosen from hydroxyl, carboxyl, cyano, nitro, $-N(R^{12}R^{12'})$, $-N(R^{12})OR^{13}$, aryl, heteroaryl, cycloalkyl, heterocyclic radical, alkyl, alkenyl, alkynyl, alkoxy, alkylcarbonyl, alkoxycarbonyl, halogen atom, trifluoromethyl, thiol, $-SR^{13'}$, $-S(O)R^{13'}$ and $-S(O_2)R^{13'}$, with $R^{13'}$ having the same definition as R^{13}, with the exception of hydrogen.

A preferred aryl radical is the phenyl radical or the 1-naphthyl, 2-naphthyl or fluorenyl radical.

Among the alkyl and alkoxy radicals substituted by an aryl radical, the benzyl, benzyloxy, phenethyl, phenylethoxy, naphthylmethyl and naphthylmethoxy radicals are particularly preferred.

Among the cycloalkyl radicals that are preferred are cyclopropyl, cyclopentyl, cyclohexyl, the adamantyl radical and radicals derived from tetralin and from decalin.

The terms "heteroaryl radical" and "heterocyclic radical" preferably mean a pyridyl, furyl, thienyl, 1-quinolyl, 2-quinolyl, tetrahydrofuryl, tetrahydropyranyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, morpholino, piperazinyl, piperidyl, pyranyl, thiopyranyl, indanyl, benzothienyl or benzofuryl radical.

For the compounds of the formulae (I) and (II) presented above, the term "geometrical isomer" means a *cis/trans* or *E/Z* isomerism. More particularly, for the compounds of the formula (I) and when R^{14} forms a bond with R^2, thus forming a double bond between the carbon atoms respectively bearing the substituents R^{14} and R^2, this double bond may be of *E* or *Z* configuration. These geometrical isomers, which may or may not be pure, alone or as a mixture, form an integral part of the compounds of the formula (I).

The term "optical isomer" includes all the forms of isomers, alone or as mixtures, arising from the presence of one or more axes and/or centres of symmetry in the molecule, and resulting in the rotation of a beam of polarised light. The term "optical isomer" more particularly includes the enantiomers and diastereoisomers, in pure form or as a mixture.

In particular, for the compounds of the formula (I), and when the substituents R^2 and R^3, on the one hand, and/or the substituents R^{16} and R^{17}, on the other hand, are different, the carbon atoms bearing these pairs of substituents are asymmetric, and thus lead to enantiomers and/or diastereoisomers. These optical isomers, which may or may not be pure, alone or as a mixture, form an integral part of the compounds of the formula (I).

Among the acids capable of forming pharmaceutically acceptable salts with the compounds of the formula (I) or of the formula (II) above, non-limiting examples that may be mentioned include hydrochloric acid, phosphoric acid, sulfuric acid, tartaric acid, citric acid, maleic acid, acetic acid, fumaric acid, alkylsulfonic acid and camphoric acid.

Among the bases capable of forming pharmaceutically acceptable salts with the compounds of the formula (I) or of the formula (II) above, non-limiting examples that may be mentioned include sodium hydroxide, potassium hydroxide, diethylamine, triethylamine, ethanolamine, diethanolamine, arginine and lysine.

The compounds of the formulae (I) and (II) above also comprise the prodrugs of these compounds.

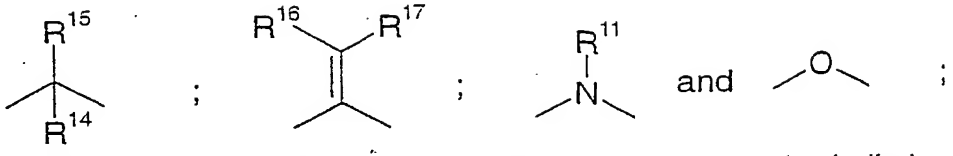
The term "prodrugs" means compounds which, once administered to the patient, are chemically and/or biologically transformed by the living body, into compounds of the formula (I) or (II).

Examples of prodrugs of compounds of the formula (I) above are those for which R^4 represents a radical -OP, in which P is a leaving group, for example a sugar residue, such as sucrose, which can thus lead to compounds in which R^4 represents -OH. Such prodrugs are included in the field of the present invention.

A large number of compounds of the formulae (I) and (II) defined above are known, especially by the patent publications and patent applications US 6 048 896, US 6 323 240, EP 0 885 869 and US 5 877 193. These publications provide the processes for the preparation of these various compounds, to which processes a person skilled in the art may refer, or may adapt, to synthesise all the compounds of the formulae (I) and (II).

According to one variant of the present invention, the compounds of the formula (I) that are preferred are those having the following characteristics, taken separately or in combination:

- W represents a divalent radical chosen from the following radicals:



- R^1 represents a radical chosen from linear or branched alkyl containing from 1 to 14 carbon atoms and optionally substituted, alkenyl, cycloalkyl, cycloalkenyl, a heterocyclic radical, an aryl radical and a heteroaryl radical;
- R^2 is chosen from hydrogen, a halogen atom, hydroxyl, thiol, carboxyl, alkyl, alkenyl, alkoxy, alkylthio, alkylcarbonyl, alkoxycarbonyl and aryl;
- R^3 is chosen from hydrogen, a halogen atom, hydroxyl, thiol, alkyl, alkenyl, alkoxy, alkylthio and aryl;
- R^2 and R^3 together also possibly forming a group $=CR^{16}R^{17}$;
- R^4 is chosen from hydroxyl, alkoxy, alkenyloxy, alkynyloxy, aryloxy, heteroaryloxy, $-N(R^{12}R^{12'})$, $-N(R^{12})OR^{13}$, linear or branched alkyl containing from 1 to 14 carbon atoms and optionally substituted, cycloalkyl, cycloalkenyl, aryl, heteroaryl and a heterocyclic radical;
- R^{12} and $R^{12'}$, which may be identical or different, are chosen, independently of each other, from hydrogen and an alkyl, alkenyl, alkynyl, alkylcarbonyl, aryl or heteroaryl radical;
- R^{13} is chosen from hydrogen and an alkyl, alkenyl, alkynyl, aryl, $-N(R^{12}R^{12'})$ or $-N(R^{12})OR^{13}$ radical;
- R^{14} is chosen from hydrogen, a halogen atom, hydroxyl, thiol, carboxyl, alkyl, alkenyl, alkoxy, alkylthio, alkylcarbonyl, alkoxycarbonyl, aryl and arylalkyl; R^{14} may also form a bond with R^2, thus forming a double bond between the carbon atoms respectively bearing the substituents R^{14} and R^2; or alternatively R^{14} forms, with R^2 and with the carbon atoms that bear them, a ring containing a total of 3, 4, 5 or 6 carbon atoms, among which 1, 2 or 3 may be replaced with an atom chosen from nitrogen and oxygen, the said ring possibly comprising one or more unsaturations in the form of (a) double bond(s), and being optionally substituted by one or more radicals, which may be identical or different, chosen from oxo, alkoxy, alkoxycarbonyl and alkylcarbonyloxy;

- R^{15} is chosen from hydrogen, a halogen atom, hydroxyl, thiol, carboxyl, alkyl, alkenyl, alkylcarbonyl, alkoxycarbonyl, alkoxy, alkylthio and aryl;
- R^{16} is chosen from hydrogen and an alkyl or aryl radical;
- R^{17} represents a hydrogen atom; and
- R^{11} is chosen from hydrogen and any protecting group for an amine function;

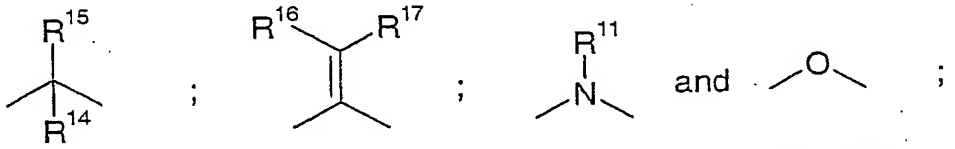
and also the possible geometrical and/or optical isomers thereof, and possible tautomeric forms thereof;

the solvates and hydrates of these compounds;

and the possible salts thereof with a pharmaceutically acceptable acid or base, or alternatively the pharmaceutically acceptable prodrugs of these compounds.

According to another variant of the present invention, this invention relates to the use of compounds of the formula (Ia) that have inhibitory activity on kynurenine 3-hydroxylase, for the preparation of a medicament for the prevention and/or treatment of diabetes. These compounds of the formula (Ia) have the general structure (I) as defined above, in which:

- W represents a divalent radical chosen from the following radicals:



- R^1 represents a radical chosen from linear or branched alkyl containing from 1 to 14 carbon atoms and optionally substituted, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, a heterocyclic radical, an aryl radical and a heteroaryl radical;
- R^2 is chosen from hydrogen, a halogen atom, hydroxyl, thiol, carboxyl, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylcarbonyl, alkoxycarbonyl, aryl, heteroaryl, cycloalkyl and a heterocyclic radical;

- R^3 is chosen from hydrogen, a halogen atom, hydroxyl, thiol, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, aryl, heteroaryl, cycloalkyl and a heterocyclic radical;
- R^2 and R^3 together also possibly forming a group $=CR^{16}R^{17}$, or alternatively forming, together with the carbon atom that bears them, a cycloalkyl radical or a heterocyclic radical;
- R^4 is chosen from hydroxyl, alkoxy, alkenyloxy, alkynyloxy, aryloxy, heteroaryloxy, $-N(R^{12}R^{12'})$, $-N(R^{12})OR^{13}$, linear or branched alkyl containing from 1 to 14 carbon atoms and optionally substituted, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl and a heterocyclic radical;
- R^{12} and $R^{12'}$, which may be identical or different, are chosen, independently of each other, from hydrogen and an alkyl, alkenyl, alkynyl, alkylcarbonyl, aryl or heteroaryl radical; or alternatively R^{12} and $R^{12'}$ may form, together with the nitrogen atom to which they are attached, a monocyclic or bicyclic heterocyclic group containing a total of 5 to 10 atoms, among which 1, 2, 3 or 4 are chosen, independently of each other, from nitrogen, oxygen and sulfur, the said heterocyclic radical also optionally comprising 1, 2, 3 or 4 double bonds and optionally being substituted by one or more chemical groups, which may be identical or different, chosen from hydroxyl, halogen atom, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, aryl, heteroaryl, heterocyclic radical and trifluoromethyl;
- R^{13} is chosen from hydrogen and an alkyl, alkenyl, alkynyl, aryl, heteroaryl, $-N(R^{12}R^{12'})$ or $-N(R^{12})OR^{13}$ radical;
- R^{14} is chosen from hydrogen, a halogen atom, hydroxyl, thiol, carboxyl, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylcarbonyl, alkoxycarbonyl, aryl, arylalkyl, heteroaryl, cycloalkyl and a heterocyclic radical;

R^{14} may also form a bond with R^2, thus forming a double bond between the carbon atoms respectively bearing the substituents R^{14} and R^2; or alternatively R^{14} forms, with R^2 and with the carbon atoms that bear them, a ring containing a total of 3, 4, 5, 6 or 7 carbon atoms, among which 1, 2 or 3 may be replaced with an atom chosen from nitrogen, oxygen and sulfur, the said ring possibly comprising one or more unsaturations in the form of (a) double bond(s), and being optionally

substituted by one or more radicals, which may be identical or different, chosen from oxo, alkoxy, alkoxycarbonyl and alkylcarbonyloxy;

- R^{15} is chosen from hydrogen, a halogen atom, hydroxyl, thiol, carboxyl, alkyl, alkenyl, alkynyl, alkylcarbonyl, alkoxycarbonyl, alkoxy, alkenyloxy, alkynyloxy, aryloxy, cycloalkyloxy, heteroaryloxy, heterocyclyloxy, alkylthio, alkenylthio, alkynylthio, arylthio, cycloalkylthio, heteroarylthio, heterocyclylthio, aryl, heteroaryl, cycloalkyl and a heterocyclic radical;
- R^{14} and R^{15} also possibly forming, together with the carbon atom that bears them, a cycloalkyl radical or a heterocyclic radical;
- R^{16} and R^{17}, which may be identical or different, are chosen, independently of each other, from hydrogen, a halogen atom, an alkyl, aryl, heteroaryl or cycloalkyl radical and a heterocyclic radical; or alternatively
R^{16} and R^{17} form, together with the carbon atom that bears them, a cycloalkyl radical or a heterocyclic radical; and
- R^{11} is chosen from hydrogen and an alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl or cycloalkylalkyl radical, and any protecting group for an amine function;
- with the restriction that when R^3, R^2 and R^{14} each represent hydrogen, then R^{15} is other than an alkyl radical, optionally substituted by aryl, heteroaryl, cycloalkyl and a heterocyclic radical;

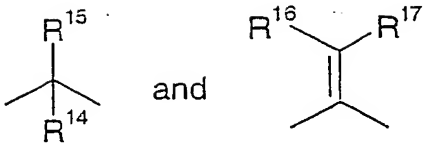
and also the possible geometrical and/or optical isomers thereof, and possible tautomeric forms thereof;

the solvates and hydrates of these compounds;

and the possible salts thereof with a pharmaceutically acceptable acid or base, or alternatively the pharmaceutically acceptable prodrugs of these compounds.

Among the compounds (Ia) defined above, the compounds that will also be preferred are those of the family (Ib) belonging to formula (I) in which:

- W represents a divalent radical chosen from the radicals:



- R^1 represents a phenyl radical, optionally substituted by 1, 2 or 3 groups chosen from cyano, nitro, phenyl, benzyl, alkyl, alkenyl containing from 2 to 4 carbon atoms, alkynyl containing from 2 to 4 carbon atoms, alkoxy, thiol -$SR^{13'}$, -$S(O)R^{13'}$ and -$S(O_2)R^{13'}$, and a halogen atom;
- R^2 is chosen from hydrogen, a halogen atom, hydroxyl, thiol, optionally substituted alkyl, in particular benzyl, alkenyl containing from 2 to 4 carbon atoms, alkoxy, alkylthio and phenyl;
- R^3 is chosen from hydrogen, a halogen atom, hydroxyl, thiol, optionally substituted alkyl, in particular benzyl, alkenyl containing from 2 to 4 carbon atoms, alkoxy, alkylthio and phenyl;
- R^2 and R^3 together also possibly forming a group $=CR^{16}R^{17}$;
- R^4 is chosen from hydroxyl, optionally substituted alkoxy, in particular benzyloxy, alkenyloxy containing from 2 to 4 carbon atoms, alkynyloxy containing from 2 to 4 carbon atoms, phenoxy, -$N(R^{12}R^{12'})$ and -$N(R^{12})OR^{13}$;
- R^{12} and $R^{12'}$, which may be identical or different, are chosen, independently of each other, from hydrogen, an optionally substituted alkyl radical, in particular benzyl, alkenyl containing from 2 to 4 carbon atoms, alkynyl containing from 2 to 4 carbon atoms, and phenyl;
- R^{13} is chosen from hydrogen, an optionally substituted alkyl radical, in particular benzyl, alkenyl containing from 2 to 4 carbon atoms, alkynyl containing from 2 to 4 carbon atoms, and phenyl;
- $R^{13'}$ is chosen from an optionally substituted alkyl radical, in particular benzyl, alkenyl containing from 2 to 4 carbon atoms, alkynyl containing from 2 to 4 carbon atoms, phenyl and -$N(R^{12}R^{12'})$;
- R^{14} is chosen from hydrogen, a halogen atom, hydroxyl, thiol, optionally substituted alkyl, in particular benzyl, alkenyl containing from 2 to 4 carbon atoms, alkoxy, alkylthio and phenyl;

R^{14} may also form a bond with R^2, thus forming a double bond between the carbon atoms respectively bearing the substituents R^{14} and R^2;

- R^{15} is chosen from hydrogen, a halogen atom, hydroxyl, thiol, optionally substituted alkyl, in particular benzyl, alkenyl containing from 2 to 4 carbon atoms, alkoxy, alkylthio and phenyl;
- R^{16} is chosen from hydrogen, a halogen atom, hydroxyl, thiol, optionally substituted alkyl, in particular benzyl, alkenyl containing from 2 to 4 carbon atoms, alkoxy, alkylthio and phenyl; and
- R^{17} represents a hydrogen atom;

with the restriction that when R^3, R^2 and R^{14} each represent hydrogen, then R^{15} is other than an alkyl radical, optionally substituted by aryl, heteroaryl, cycloalkyl and a heterocyclic radical;

and also the possible geometrical and/or optical isomers thereof, and the possible tautomeric forms thereof;

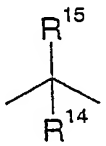
the solvates and hydrates of these compounds;

and also the possible salts thereof with a pharmaceutically acceptable acid or base, or alternatively the pharmaceutically acceptable prodrugs of these compounds.

In the vast majority, the compounds (Ib) defined above show entirely advantageous inhibitory activity on kynurenine 3-hydroxylase. As a result, these compounds are most particularly preferred and simple to use for any of the abovementioned uses according to the invention.

According to another variant of the invention, this invention relates to the use of compounds of the family (Ic) as kynurenine 3-hydroxylase inhibitors in any of the abovementioned uses according to the invention. These compounds of family (Ic) have the general structure (I) as defined above, in which:

- W represents the divalent radical:



- R^1 represents a radical chosen from linear or branched alkyl containing from 1 to 14 carbon atoms and optionally substituted, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, a heterocyclic radical, an aryl radical and a heteroaryl radical;
- R^2 represents hydrogen;
- R^3 represents hydrogen;
- R^4 is chosen from hydroxyl, alkoxy, alkenyloxy, alkynyloxy, aryloxy, heteroaryloxy, $-N(R^{12}R^{12'})$ and $-N(R^{12})OR^{13}$;
- R^{12} and $R^{12'}$, which may be identical or different, are chosen, independently of each other, from hydrogen and an alkyl, alkenyl, alkynyl, alkylcarbonyl, aryl or heteroaryl radical; or alternatively R^{12} and $R^{12'}$ may form, together with the nitrogen atom to which they are attached, a monocyclic or bicyclic heterocyclic group containing a total of 5 to 10 atoms, among which 1, 2, 3 or 4 are chosen, independently of each other, from nitrogen, oxygen and sulfur, the said heterocyclic radical also optionally comprising 1, 2, 3 or 4 double bonds and optionally being substituted by one or more chemical groups, which may be identical or different, chosen from hydroxyl, halogen atom, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, aryl, heteroaryl, heterocyclic radical and trifluoromethyl;
- R^{13} is chosen from hydrogen and an alkyl, alkenyl, alkynyl, aryl, heteroaryl, $-N(R^{12}R^{12'})$ or $-N(R^{12})OR^{13}$ radical;
- R^{14} represents hydrogen;
- R^{15} represents hydrogen;

and also the possible geometrical and/or optical isomers thereof, and the possible tautomeric forms thereof;

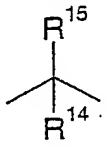
the solvates and hydrates of these compounds;

and also the possible salts thereof with a pharmaceutically acceptable acid or base, or alternatively the pharmaceutically acceptable prodrugs of these compounds.

According to another variant, the invention relates to the use of compounds of the family (Id) as kynurenine 3-hydroxylase inhibitors in any of the above-

mentioned uses according to the invention, the said compounds (Id) having the general structure (I) as defined above, in which:

- W represents the divalent radical:



- R^1 represents a radical chosen from linear or branched alkyl containing from 1 to 14 carbon atoms and optionally substituted, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, a heterocyclic radical, an aryl radical and a heteroaryl radical;
- R^2 represents hydrogen;
- R^3 represents hydrogen;
- R^4 is chosen from hydroxyl, alkoxy, alkenyloxy, alkynyloxy, aryloxy, heteroaryloxy, $-N(R^{12}R^{12'})$ and $-N(R^{12})OR^{13}$;
- R^{12} and $R^{12'}$, which may be identical or different, are chosen, independently of each other, from hydrogen and an alkyl, alkenyl, alkynyl, alkylcarbonyl, aryl or heteroaryl radical; or alternatively R^{12} and $R^{12'}$ may form, together with the nitrogen atom to which they are attached, a monocyclic or bicyclic heterocyclic group containing a total of 5 to 10 atoms, among which 1, 2, 3 or 4 are chosen, independently of each other, from nitrogen, oxygen and sulfur, the said heterocyclic radical also optionally comprising 1, 2, 3 or 4 double bonds and optionally being substituted by one or more chemical groups, which may be identical or different, chosen from hydroxyl, halogen atom, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, aryl, heteroaryl, heterocyclic radical and trifluoromethyl;
- R^{13} is chosen from hydrogen and an alkyl, alkenyl, alkynyl, aryl, heteroaryl, $-N(R^{12}R^{12'})$ or $-N(R^{12})OR^{13}$ radical;
- R^{14} represents hydrogen; and
- R^{15} is chosen from hydroxyl, alkoxy, alkenyloxy, alkynyloxy, aryloxy, cycloalkyloxy, heteroaryloxy and heterocyclyloxy;

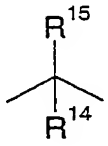
and also the possible geometrical and/or optical isomers thereof, and the possible tautomeric forms thereof;

the solvates and hydrates of these compounds;

and also the possible salts thereof with a pharmaceutically acceptable acid or base, or alternatively the pharmaceutically acceptable prodrugs of these compounds.

Another preferred group of compounds consists of the compounds of family (Ie) as kynurenine 3-hydroxylase inhibitors in any of the abovementioned uses according to the invention, the said compounds (Ie) belonging to the general formula (I) as defined above, in which:

- W represents the divalent radical:



- R^1 represents a radical chosen from linear or branched alkyl containing from 1 to 14 carbon atoms and optionally substituted, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, a heterocyclic radical, an aryl radical and a heteroaryl radical;
- R^2 and R^{14} together form a bond, thus forming a double bond between the carbon atoms respectively bearing R^2 and R^{14};
- R^3 represents hydrogen;
- R^4 is chosen from hydroxyl, alkoxy, alkenyloxy, alkynyloxy, aryloxy, heteroaryloxy, $-N(R^{12}R^{12'})$ and $-N(R^{12})OR^{13}$;
- R^{12} and $R^{12'}$, which may be identical or different, are chosen, independently of each other, from hydrogen and an alkyl, alkenyl, alkynyl, alkylcarbonyl, aryl or heteroaryl radical; or alternatively R^{12} and $R^{12'}$ may form, together with the nitrogen atom to which they are attached, a monocyclic or bicyclic heterocyclic group containing a total of 5 to 10 atoms, among which 1, 2, 3 or 4 are chosen, independently of each other, from nitrogen, oxygen and sulfur, the said heterocyclic radical also optionally comprising 1, 2, 3 or 4 double bonds and optionally being substituted by one or more chemical groups, which may be identical or different, chosen from hydroxyl, halogen atom, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, aryl, heteroaryl, heterocyclic radical and trifluoromethyl;
- R^{13} is chosen from hydrogen and an alkyl, alkenyl, alkynyl, aryl, heteroaryl, $-N(R^{12}R^{12'})$ or $-N(R^{12})OR^{13}$ radical; and

- R^{15} represents hydrogen;

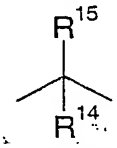
and also the possible geometrical and/or optical isomers thereof, and the possible tautomeric forms thereof;

the solvates and hydrates of these compounds;

and also the possible salts thereof with a pharmaceutically acceptable acid or base, or alternatively the pharmaceutically acceptable prodrugs of these compounds.

According to another variant of the present invention, this invention relates to the use of compounds of family (If) as kynurenine 3-hydroxylase inhibitors in any of the abovementioned uses according to the invention, the said compounds (If) belonging to the general formula (I) as defined above, in which:

- W represents the divalent radical:



- R^1 represents a radical chosen from linear or branched alkyl containing from 1 to 14 carbon atoms and optionally substituted, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, a heterocyclic radical, an aryl radical and a heteroaryl radical;
- R^2 and R^{14} together form a bond, thus forming a double bond between the carbon atoms respectively bearing R^2 and R^{14};
- R^3 represents hydrogen;
- R^4 is chosen from hydroxyl, alkoxy, alkenyloxy, alkynyloxy, aryloxy, heteroaryloxy, $-N(R^{12}R^{12'})$ and $-N(R^{12})OR^{13}$;
- R^{12} and $R^{12'}$, which may be identical or different, are chosen, independently of each other, from hydrogen and an alkyl, alkenyl, alkynyl, alkylcarbonyl, aryl or heteroaryl radical; or alternatively R^{12} and $R^{12'}$ may form, together with the nitrogen atom to which they are attached, a monocyclic or bicyclic heterocyclic group containing a total of 5 to 10 atoms, among which 1, 2, 3 or 4 are chosen, independently of each other, from nitrogen, oxygen and sulfur, the said heterocyclic radical also optionally comprising 1, 2, 3 or 4 double bonds and optionally being substituted by one or more chemical groups, which may be

identical or different, chosen from hydroxyl, halogen atom, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, aryl, heteroaryl, heterocyclic radical and trifluoromethyl;

- R^{13} is chosen from hydrogen and an alkyl, alkenyl, alkynyl, aryl, heteroaryl; $-N(R^{12}R^{12'})$ or $-N(R^{12})OR^{13}$ radical; and
- R^{15} is chosen from hydroxyl, alkoxy, alkenyloxy, alkynyloxy, aryloxy, cycloalkyloxy, heteroaryloxy and heterocyclyloxy;

and also the possible geometrical and/or optical isomers thereof, and the possible tautomeric forms thereof;

the solvates and hydrates of these compounds;

and also the possible salts thereof with a pharmaceutically acceptable acid or base, or alternatively the pharmaceutically acceptable prodrugs of these compounds.

Among the compounds of the general formula (I), and according to another variant of the invention, the compounds are chosen from the family of compounds (Ig) consisting of:

- 4-(4'-methylcyclohexyl)-4-oxobutanoic acid;
- 2-hydroxy-4-(3',4'-difluorophenyl)-4-oxobutanoic acid;
- 2-methoxy-4-(3',4'-difluorophenyl)-4-oxobutanoic acid;
- 2-hydroxy-3-methyl-4-(3',4'-dichlorophenyl)-4-oxobutanoic acid;
- 2-hydroxy-3-phenyl-4-(3',4'-dichlorophenyl)-4-oxobutanoic acid;
- 2-hydroxy-3-benzyl-4-(3',4'-dichlorophenyl)-4-oxobutanoic acid;
- 2-methyl-4-(3',4'-dichlorophenyl)-4-oxobutanoic acid;
- 2-methyl-4-(3',4'-difluorophenyl)-4-oxobutanoic acid;
- 2-chloro-4-(3',4'-dichlorophenyl)-4-oxobutanoic acid;
- 2-chloro-4-(3',4'-difluorophenyl)-4-oxobutanoic acid;
- 2-fluoro-4-(3',4'-dichlorophenyl)-4-oxobutanoic acid;
- 2-fluoro-4-(3',4'-difluorophenyl)-4-oxobutanoic acid;
- 2-thiomethyl-4-(3',4'-dichlorophenyl)-4-oxobutanoic acid;
- 2-methylidene-4-(3',4'-dichlorophenyl)-4-oxobutanoic acid;
- 2-phenyl-4-(3',4'-dichlorophenyl)-4-oxobutanoic acid;
- 2-benzyl-4-(3',4'-dichlorophenyl)-4-oxobutanoic acid;

- 3-methyl-4-(3',4'-dichlorophenyl)-4-oxobutanoic acid;
- 3-phenyl-4-(3',4'-dichlorophenyl)-4-oxobutanoic acid;
- 3-benzyl-4-(3',4'-dichlorophenyl)-4-oxobutanoic acid;
- methyl (*R,S*)-2-hydroxy-4-(3',4'-dichlorophenyl)-4-oxobutanoate;
- methyl (*R,S*)-2-benzyl-4-(3',4'-dichlorophenyl)-4-oxobutanoate;
- 4-(3'-fluorophenyl)-4-oxo-2-butenoic acid;
- 4-(3'-chlorophenyl)-4-oxo-2-butenoic acid;
- 4-(3'-nitrophenyl)-4-oxo-2-butenoic acid;
- 4-(3'-fluoro-4'-methoxyphenyl)-4-oxo-2-butenoic acid;
- 2-methyl-4-(3',4'-dichlorophenyl)-4-oxo-2-butenoic acid;
- 3-methyl-4-(3',4'-dichlorophenyl)-4-oxo-2-butenoic acid;
- 3-phenyl-4-(3',4'-dichlorophenyl)-4-oxo-2-butenoic acid;
- 3-benzyl-4-(3',4'-dichlorophenyl)-4-oxo-2-butenoic acid;
- 2,3-dimethyl-4-(3',4'-dichlorophenyl)-4-oxo-2-butenoic acid;
- 2-hydroxy-4-(3'-chlorophenyl)-4-oxo-2-butenoic acid;
- 2-hydroxy-4-(3'-fluorophenyl)-4-oxo-2-butenoic acid;
- 2-hydroxy-4-(3',4'-dichlorophenyl)-4-oxo-2-butenoic acid;
- 2-hydroxy-4-(3',4'-difluorophenyl)-4-oxo-2-butenoic acid; and
- 2-hydroxy-4-(3'-chloro-4'-methoxyphenyl)-4-oxo-2-butenoic acid;

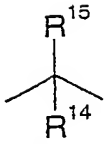
and also the possible geometrical and/or optical isomers thereof, and the possible tautomeric forms thereof;

the solvates and hydrates of these compounds;

and also the possible salts thereof with a pharmaceutically acceptable acid or base, or alternatively the pharmaceutically acceptable prodrugs of these compounds.

According to another variant of the invention, a family of compounds (Ih) having the abovementioned general structure (I) is defined, for which:

- W represents the divalent radical:



;

- R^1, R^2, R^3, R^4, R^{12}, $R^{12'}$, R^{13} and R^{14} are as defined above; and
- R^{15} is chosen from a thiol, alkylthio, alkenylthio, alkynylthio, arylthio, cycloalkylthio, heteroarylthio or heterocyclylthio radical;

with the restriction that when R^2, R^3 and R^{14} each represent hydrogen, then R^{15} cannot represent a thiol or alkylthio radical;

and also the possible geometrical and/or optical isomers thereof, and the possible tautomeric forms thereof;

the solvates and hydrates of these compounds;

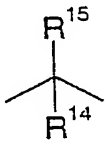
and also the possible salts thereof with a pharmaceutically acceptable acid or base, or alternatively the pharmaceutically acceptable prodrugs of these compounds.

The compounds of family (Ih) form a particularly preferred aspect of the present invention. The compounds of family (Ih) have entirely noteworthy hypoglycaemiant properties and, in this respect, are useful as kynurenine 3-hydroxylase inhibitors in any of the abovementioned uses according to the invention.

In addition, the compounds of family (Ih) show inhibitory activity on kynurenine 3-hydroxylase that may be linked to the observed effect on the increase in the mass of beta cells, especially in the case of diabetes.

A preferred subfamily of the compounds of the family (Ih) consists of the compounds of the family (Ii) belonging to the general formula (I) in which:

- W represents the divalent radical:



;

- R^1 represents an aryl radical;
- R^2 represent hydrogen, or forms a bond with R^{14};
- R^3 represents hydrogen;

- R^4 is chosen from hydroxyl, alkoxy, alkenyloxy, alkynyloxy, aryloxy, heteroaryloxy, $-N(R^{12}R^{12'})$ and $-N(R^{12})OR^{13}$;
- R^{12} and $R^{12'}$, which may be identical or different, are chosen, independently of each other, from hydrogen and an alkyl, alkenyl, alkynyl, alkylcarbonyl, aryl or heteroaryl radical; or alternatively R^{12} and $R^{12'}$ may form, together with the nitrogen atom to which they are attached, a monocyclic or bicyclic heterocyclic group containing a total of 5 to 10 atoms, among which 1, 2, 3 or 4 are chosen, independently of each other, from nitrogen, oxygen and sulfur, the said heterocyclic radical also optionally comprising 1, 2, 3 or 4 double bonds and optionally being substituted by one or more chemical groups, which may be identical or different, chosen from hydroxyl, halogen atom, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, aryl, heteroaryl, heterocyclic radical and trifluoromethyl;
- R^{13} is chosen from hydrogen and an alkyl, alkenyl, alkynyl, aryl, heteroaryl, $-N(R^{12}R^{12'})$ or $-N(R^{12})OR^{13}$ radical;
- R^{14} represents hydrogen, or forms a bond with R^2; and
- R^{15} represents an arylthio radical;

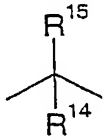
and also the possible geometrical and/or optical isomers thereof, and the possible tautomeric forms thereof;

the solvates and hydrates of these compounds;

and also the possible salts thereof with a pharmaceutically acceptable acid or base, or alternatively the pharmaceutically acceptable prodrugs of these compounds.

Among the compounds of family (Ii) that are also preferred are the compounds of family (Ij) corresponding to the general formula (I), in which:

- W represents the divalent radical:



;

- R^1 represents a phenyl radical;
- R^2 represents hydrogen;

- R^3 represents hydrogen;
- R^4 is chosen from hydroxyl and an alkoxy radical;
- R^{14} represents hydrogen; and
- R^{15} represents a phenylthio radical;

and also the possible geometrical and/or optical isomers thereof, and the possible tautomeric forms thereof;

the solvates and hydrates of these compounds;

and also the possible salts thereof with a pharmaceutically acceptable acid or base, or alternatively the pharmaceutically acceptable prodrugs of these compounds.

By way of illustration, examples of compounds of family (Ih) are:

- compound Ih-1:

2-(2'-naphthylthio)-4-phenyl-4-oxobutanoic acid;

- compound Ih-2:

2-phenylthio-4-phenyl-4-oxobutanoic acid;

- compound Ih-3:

2-(4'-fluorophenylthio)-4-phenyl-4-oxobutanoic acid;

- compound Ih-4:

2-(4'-chlorophenylthio)-4-phenyl-4-oxobutanoic acid;

compound Ih-5:

2-(4'-methylphenylthio)-4-phenyl-4-oxobutanoic acid;

- compound Ih-6:

2-(4'-methoxyphenylthio)-4-phenyl-4-oxobutanoic acid;

- compound Ih-7:

2-cyclohexylthio-4-phenyl-4-oxobutanoic acid;

- compound Ih-8:

2-benzylthio-4-phenyl-4-oxobutanoic acid;

- compound Ih-9:

ethyl 2-phenylthio-4-phenyl-4-oxobutanoate;

- compound Ih-10:

ethyl 2-(4'-fluorophenylthio)-4-phenyl-4-oxobutanoate;

- compound Ih-11:

ethyl 2-(4'-chlorophenylthio)-4-phenyl-4-oxobutanoate;

- compound Ih-12:

ethyl 2-(4'-methylphenylthio)-4-phenyl-4-oxobutanoate;

- compound Ih-13:

ethyl 2-(4'-methoxyphenylthio)-4-phenyl-4-oxobutanoate;

- compound Ih-14:

ethyl 2-(2'-naphthylthio)-4-phenyl-4-oxobutanoate;

- compound Ih-15:

ethyl 2-cyclohexylthio-4-phenyl-4-oxobutanoate;

- compound Ih-16:

ethyl 2-benzylthio-4-phenyl-4-oxobutanoate;

- compound Ih-17:

2-phenylthio-4-(4'-methoxyphenyl)-4-oxobutanoic acid;

- compound Ih-18:

2-(4'-fluorophenylthio)-4-(4'-methoxyphenyl)-4-oxobutanoic acid;

- compound Ih-19:

2-(4'-chlorophenylthio)-4-(4'-methoxyphenyl)-4-oxobutanoic acid;

- compound Ih-20:

2-(4'-methylphenylthio)-4-(4'-methoxyphenyl)-4-oxobutanoic acid;

- compound Ih-21:

2-(4'-methoxyphenylthio)-4-(4'-methoxyphenyl)-4-oxobutanoic acid;

- compound Ih-22:

2-(2'-naphthylthio)-4-(4'-methoxyphenyl)-4-oxobutanoic acid;

- compound Ih-23:

2-cyclohexylthio-4-(4'-methoxyphenyl)-4-oxobutanoic acid;

- compound Ih-24:

2-benzylthio-4-(4'-methoxyphenyl)-4-oxobutanoic acid;

- compound Ih-25:

2-phenylthio-4-(4'-chlorophenyl)-4-oxobutanoic acid;

- compound Ih-26:

2-(4'-fluorophenylthio)-4-(4'-chlorophenyl)-4-oxobutanoic acid;

- compound Ih-27:

2-(4'-chlorophenyl)-4-(4'-chlorophenyl)-4-oxobutanoic acid;

- compound Ih-28:

2-(4'-methylphenylthio)-4-(4'-chlorophenyl)-4-oxobutanoic acid;

- compound Ih-29:

2-(4'-methoxyphenylthio)-4-(4'-chlorophenyl)-4-oxobutanoic acid;

- compound Ih-30:

2-(2'-naphthylthio)-4-(4'-chlorophenyl)-4-oxobutanoic acid;

and 2-carboxymethylthio-4-phenyl-4-oxobutanoic acid (f);

and also the possible geometrical and/or optical isomers thereof, and the possible tautomeric forms thereof;

the solvates and hydrates of these compounds;

and also the possible salts thereof with a pharmaceutically acceptable acid or base, or alternatively the pharmaceutically acceptable prodrugs of these compounds.

It has been discovered, unexpectedly, that the compounds of the formula (I) according to the variants described above show particularly advantageous activity when R^1 is aryl or heteroaryl; these groups are thus most particularly preferred.

According to one particular aspect of the invention, among the different variants of the formula (I) above that are preferred are the compounds for which, when R^2=R^3=H, W is other than $-CH(CH_2-X)-$ in which X = alkyl, aryl, cycloalkyl, pyridyl, pyrimidyl, pyrrolyl, furyl, thienyl, tetrahydrofuryl, tetrahydropyranyl, piperidyl or pyrrolidinyl, which are optionally substituted.

According to another particular aspect of the invention, the compounds of the formula (I) are different from:

- racemic 2-benzyl-4-(4-methoxyphenyl)-4-oxobutanoic acid and the R and S isomers thereof;

- racemic 2-benzyl-4-(4-fluorophenyl)-4-oxobutanoic acid and the R and S isomers thereof;
- 2-cyclohexylmethyl-4-(4-methoxyphenyl)-4-oxobutanoic acid;
- 2-benzyl-4-phenyl-4-oxobutanoic acid;
- 2-(β-naphthylmethyl)-4-phenyl-4-oxobutanoic acid;
- 2-benzyl-4-(β-naphthyl)-4-oxobutanoic acid;
- 2-[(4-chlorophenyl)methyl]-4-(4-methoxyphenyl)-4-oxobutanoic acid;
- 2-benzyl-4-(4-methylphenyl)-4-oxobutanoic acid;
- 4-(4-fluorophenyl)-2-[(4-methoxyphenyl)methyl]-4-oxobutanoic acid;
- 2-benzyl-4-(3,4-methylenedioxyphenyl)-4-oxobutanoic acid;
- 2-benzyl-4-cyclohexyl-4-oxobutanoic acid;
- 4-phenyl-2-[(tetrahydrofur-2-yl)methyl]-4-oxobutanoic acid.

Among the compounds of the formula (II) defined above that are preferred are the compounds of the family (IIa) corresponding to the general formula (II) in which:

- R^5, R^6, R^7 and R^8 are as defined above;
- R^9 represents hydrogen; and
- R^{10} is chosen from a phenyl radical, optionally substituted in position 3 and/or 4 with an alkyl or alkoxy radical, preferably methyl or methoxy, and a naphthyl radical;

and also the possible geometrical and/or optical isomers thereof, and the possible tautomeric forms thereof;
the solvates and hydrates of these compounds;
and also the possible salts thereof with a pharmaceutically acceptable acid or base, or alternatively the pharmaceutically acceptable prodrugs of these compounds.

Another family (IIb) of compounds of the formula (II) is represented by the compounds of the general formula (II) in which:

- R^5, R^6, R^7 and R^8, which may be identical or different, are chosen, independently of each other, from hydrogen, a halogen atom, a nitro radical and a trifluoromethyl radical;

the radicals R^6 and R^7 also possibly forming, together with the carbon atoms to which they are attached, a benzene ring, optionally substituted by one or more groups, which may be identical or different, chosen from a halogen atom and a trifluoromethyl, nitro or alkoxy radical; and

- R^9 and R^{10} are as defined above;

and also the possible geometrical and/or optical isomers thereof, and the possible tautomeric forms thereof;

the solvates and hydrates of these compounds;

and also the possible salts thereof with a pharmaceutically acceptable acid or base, or alternatively the pharmaceutically acceptable prodrugs of these compounds.

According to one preferred variant of the invention, the compounds of the formula (II) are chosen from the list consisting of:

- 4-methoxy-N-(4-naphthalen-2-ylthiazol-2-yl)benzenesulfonamide;
- 4-amino-N-[4-(3-nitrophenyl)thiazol-2-yl]benzenesulfonamide;
- 4-methyl-N-[4-(3-nitrophenyl)thiazol-2-yl]benzenesulfonamide;
- 3,4-dimethoxy-N-[4-(3-nitrophenyl)thiazol-2-yl]benzenesulfonamide;
- 4-methoxy-N-[4-(3-nitrophenyl)thiazol-2-yl]benzenesulfonamide;
- 2-naphthalenesulfonic acid [4-(3-nitrophenyl)thiazol-2-yl]benzenesulfonamide;
- N-[4-(2-fluoro-5-trifluoromethylphenyl)thiazol-2-yl]-4-methylbenzenesulfonamide;
- N-[4-(3-fluoro-5-trifluoromethylphenyl)thiazol-2-yl]-4-methylbenzenesulfonamide;
- 4-methyl-N-[4-(4-nitrophenyl)thiazol-2-yl]benzenesulfonamide;
- 4-amino-N-[4-(2-fluoro-5-trifluoromethylphenyl)thiazol-2-yl]benzenesulfonamide; and

- 3,4-dimethoxy-N-[4-(2-fluoro-5-trifluoromethylphenyl)thiazol-2-yl]benzene-sulfenamide;

and also the possible geometrical and/or optical isomers thereof, and the possible tautomeric forms thereof;

the solvates and hydrates of these compounds;

and also the possible salts thereof with a pharmaceutically acceptable acid or base, or alternatively the pharmaceutically acceptable prodrugs of these compounds.

Among the variants of the formulae (I) and (II) described above, the compounds that are preferred according to the invention are those with substantial inhibitory activity on kynurenine 3-hydroxylase as defined above.

The compounds of the formulae (I) and (II) defined above are useful as kynurenine 3-hydroxylase inhibitors for any of the uses according to the invention defined above.

The pharmaceutical uses or compositions according to the invention thus comprise as active principle a pharmacologically effective amount of at least one kynurenine 3-hydroxylase inhibitor, preferably a compound of the formula (I) or of the formula (II), alone or in combination with one or more fillers, vehicles, colorants or sweeteners, i.e. any suitable and pharmaceutically acceptable non-toxic, inert excipient usually used in the production of pharmaceutical compositions.

The said compositions are administered to patients in need thereof, i.e. to individuals whose condition might be prevented or improved by increasing the number of islets of Langerhans cells.

According to the invention, the kynurenine 3-hydroxylase inhibitors may be useful in combination with an active agent usually used in the treatment of diabetes, as a main active principle or as an adjuvant and/or potentiator of the said agent.

The pharmaceutical compositions thus obtained will be in various forms, the most advantageous being gel capsules, suppositories, injectable or drinkable

solutions, patches, plain, sugar-coated, film-coated or sublingual tablets, sachets, packets, lozenges, creams, ointments, dermal gels, aerosols, etc.

The working dose may be adapted according to the nature and severity of the pathology to be treated, the administration route and also the patient's age and weight. In general, the unit dose will range between 5 mg and 2000 mg per day, in one or more dosage intakes, advantageously between 10 mg and 1000 mg, for example between 50 mg and 800 mg.

It has been discovered, surprisingly, that the kynurenine 3-hydroxylase inhibitors have the twofold activity of controlling the secretion of both glucagon and insulin. Specifically, in the absence of glucose, the secretion of glucagon is stimulated whereas that of insulin is not. In the presence of glucose, the secretion of insulin is potentiated whereas the secretion of glucagon remains normally inhibited.

Such a dual activity affords a considerable improvement over the processes for the treatment of diabetes currently used. Specifically, the risks of hypoglycaemia are very greatly reduced, or even virtually nonexistent, even when the prescribed doses and/or number of administrations are exceeded or have been poorly controlled.

The abovementioned uses according to the invention thus make it possible to minimise or eliminate the risk of hypoglycaemia.

Among the compounds of the formula (I) that have inhibitory activity on kynurenine 3-hydroxylase, non-limiting examples that may be mentioned include:

- 4-(3',4'-dichlorophenyl)-4-oxobutanoic acid;
- 4-(3',4'-difluorophenyl)-4-oxobutanoic acid;
- methyl 4-(3',4'-dichlorophenyl)-4-oxobutanoate;
- (*R,S*)-2-hydroxy-4-(3'-chlorophenyl)-4-oxobutanoic acid;
- (*R,S*)-2-hydroxy-4-(3'-fluorophenyl)-4-oxobutanoic acid;

- (*R,S*)-2-hydroxy-4-(3'-nitrophenyl)-4-oxobutanoic acid;
- (*R,S*)-2-hydroxy-4-(3',4'-dichlorophenyl)-4-oxobutanoic acid;
- (*S*)-2-hydroxy-4-(3',4'-dichlorophenyl)-4-oxobutanoic acid;
- (*R*)-2-hydroxy-4-(3',4'-dichlorophenyl)-4-oxobutanoic acid;
- methyl (*R,S*)-2-hydroxy-4-(3',4'-dichlorophenyl)-4-oxobutanoate;
- (*R,S*)-2-hydroxy-4-(3',4'-difluorophenyl)-4-oxobutanoic acid;
- (*R,S*)-2-methoxy-4-(3',4'-difluorophenyl)-4-oxobutanoic acid;
- (*R,S*)-2-methoxy-4-(3',4'-dichlorophenyl)-4-oxobutanoic acid;
- (*R,S*)-2-methyl-4-(3',4'-dichlorophenyl)-4-oxobutanoic acid;
- (*R,S*)-3-methyl-4-(3',4'-dichlorophenyl)-4-oxobutanoic acid;
- 2-hydroxy-3-benzyl-4-(3',4'-dichlorophenyl)-4-oxobutanoic acid;
- (*R,S*)-2-methyl-4-(3',4'-difluorophenyl)-4-oxobutanoic acid;
- (*R,S*)-2-chloro-4-(3',4'-dichlorophenyl)-4-oxobutanoic acid;
- (*R,S*)-2-methylidene-4-(3',4'-dichlorophenyl)-4-oxobutanoic acid;
- (*R,S*)-3-phenyl-4-(3',4'-dichlorophenyl)-4-oxobutanoic acid;
- methyl (*R,S*)-2-benzyl-4-(3',4'-dichlorophenyl)-4-oxobutanoate;
- (*R,S*)-2-phenyl-4-(3',4'-dichlorophenyl)-4-oxobutanoic acid;
- (*R,S*)-2-benzyl-4-(3',4'-dichlorophenyl)-4-oxobutanoic acid;
- (*E*)-4-(3',4'-dichlorophenyl)-4-oxo-2-butenoic acid;
- (*E*)-4-(3',4'-difluorophenyl)-4-oxo-2-butenoic acid;
- (*E*)-4-(3'-fluorophenyl)-4-oxo-2-butenoic acid;
- (*E*)-4-(3'-chlorophenyl)-4-oxo-2-butenoic acid;
- (*E*)-4-(3'-nitrophenyl)-4-oxo-2-butenoic acid;
- (*E*)-2-methyl-4-(3',4'-dichlorophenyl)-4-oxo-2-butenoic acid;
- 3-methyl-4-(3',4'-dichlorophenyl)-4-oxo-2-butenoic acid;
- 3-benzyl-4-(3',4'-dichlorophenyl)-4-oxo-2-butenoic acid;
- (*E*)-2-hydroxy-4-(3'-chlorophenyl)-4-oxo-2-butenoic acid;
- (*E*)-2-hydroxy-4-(3'-fluorophenyl)-4-oxo-2-butenoic acid;
- (*E*)-2-hydroxy-4-(4'-chlorophenyl)-4-oxo-2-butenoic acid;
- (*E*)-2-hydroxy-4-(3',4'-dichlorophenyl)-4-oxo-2-butenoic acid;
- (*E*)-2-hydroxy-4-(3',4'-difluorophenyl)-4-oxo-2-butenoic acid;
- methyl (*E*)-2-hydroxy-4-(3',4'-dichlorophenyl)-4-oxo-2-butenoate; and

- ethyl (*E*)-2-hydroxy-4-(3',4'-dichlorophenyl)-4-oxo-2-butenoate;

and also the possible geometrical and/or optical isomers thereof, and the possible tautomeric forms thereof;

the solvates and hydrates of these compounds;

and also the possible salts thereof with a pharmaceutically acceptable acid or base, or alternatively the pharmaceutically acceptable prodrugs of these compounds.

The invention also relates to a process for increasing the number of islets of Langerhans cells, comprising the administration, to a patient requiring it, of a dose of one or more compounds that inhibit kynurenine 3-hydroxylase of the formula (I) or of the formula (II) defined above, such that it produces a substantial inhibition of kynurenine 3-hydroxylase in the patient.

In particular, the process defined above allows the prevention or treatment of diabetes and/or its complications, especially in the case of patients presenting the characteristics of the diabetes pathology, without this pathology yet having been declared. The criteria for diagnosing this pathology are defined, for example, in *Diabetes Care*, vol. 25, suppl. 1, January 2002.

Among the complications that may be mentioned especially are arterial hypertension, diabetes-related inflammatory processes, diabetic nephropathy, macroangiopathy and microangiopathy, peripheral diabetic neuropathy and retinopathy of diabetic origin.

As mentioned previously, the compounds of the formulae (I) and (II) defined above have been found to be useful in the prevention and/or treatment of diabetes and its complications, by increasing the number of islets of Langerhans cells, according to a mode of action that is hitherto unknown in this therapeutic field.

The invention also relates to a process for manufacturing medicaments for increasing the number of islets of Langerhans cells, especially for the the treatment and/or prevention of diabetes and its complications, by inhibiting kynurenine 3-hydroxylase, in which at least one compound of the formula (I) or (II) is sub-

jected to an *in vitro* test of inhibition of kynurenine 3-hydroxylase, and the molecules responding positively to the said tests are then conditioned in the form of a pharmaceutical composition, optionally with addition of a pharmaceutically acceptable filler or vehicle.

Finally, the invention also relates to a process for screening candidate compounds for activity in increasing the number of islets of Langerhans cells, especially for the the treatment and/or prevention of diabetes or its complications, by inhibiting kynurenine 3-hydroxylase, the said candidates not corresponding to formula (I) or (II), in which process the candidate compounds are subjected to an *in vitro* test of inhibition of kynurenine 3-hydroxylase, and the candidate that has responded positively to this test is selected.

Among the candidates that will be preferred are the compounds already known as having antidiabetic activity.

The examples that follow illustrate, without placing any limitation of any kind on the invention, some of the subjects of the invention, in particular the preparation processes and the activities of some of the compounds described above in antidiabetic activity tests and tests of inhibition of kynurenine 3-hydroxylase.

Preparation example

Preparation of 2-(2'-naphthylthio)-4-phenyl-4-oxobutanoic acid (compound Ih-1)

7.04 g (0.04 mol) of commercial 3-benzoylacrylic acid are dissolved in 90 mL of methylene chloride. 2-Naphthalenethiol (0.04 mol; 1 equivalent) is then added. The reaction medium is left for 20 hours at 20°C and then concentrated under vacuum. The crude solid product isolated is then triturated from isopropyl ether, filtered off by suction and recrystallised from isopropyl ether.

Isolated weight: 5.55 g; yield = 41%; melting point = 146-149°C (capillary melting point).

Proton NMR (200 MHz, solvent: deuterated DMSO): 3.74 ppm, multiplet, 2H; 4.43 ppm, broad singlet, 1H; 7.9 ppm, multiplet, 12H arom.; 12.9 ppm, COOH).

Infrared spectrometry (cm^{-1}): 1702.8; 1680.7; 1595.0; 1435.2; 1326.6; 1217.6.

TLC analysis:

silica, eluent: methylcyclohexane, ethyl acetate, acetic acid (50/45/5): Rf: 0.53.

The compounds of the family (Ih) as defined above were prepared according to a similar process.

Preparation of ethyl 2-(4-methoxyphenylthio)-4-phenyl-4-oxobutanoate (compound Ih-13)

0.408 g of commercial ethyl benzoylacrylate (0.002 mol) is dissolved in 6 ml of methylene chloride in a round-bottomed flask under argon. 0.280 g (1 equivalent) of 4-methoxythiophenol is then added.

The reaction medium is left at 20°C for 72 hours and then concentrated under vacuum.

The crude oil isolated is then purified on a column of silica (eluent: 90/10 cyclohexane/ethyl acetate).

Isolated weight: 0.390 g; yield = 56.6%; oil.

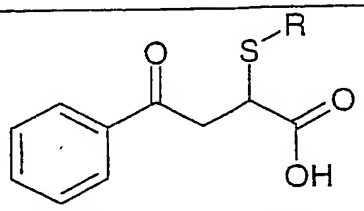
Proton NMR (200 MHz, solvent: deuterated chloroform):

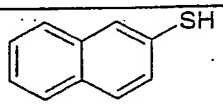
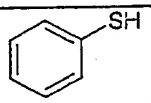
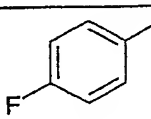
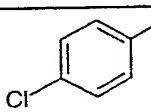
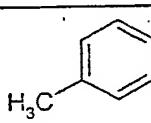
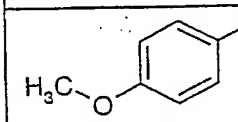
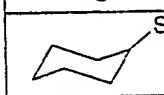
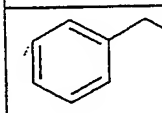
1.06 ppm, triplet, 3H; 3.41 ppm, multiplet, 2H; 3.66 ppm, singlet, 3H; 4.01 ppm, multiplet, 3H; 6.72 ppm, doublet, 2H arom.; 7.32 ppm, multiplet, 5H arom.; 7.78 ppm, doublet, 2H arom.

Infrared spectrometry (cm^{-1}): 1730.6 ; 1685.1; 1493.9; 1448.8; 1287.6; 1248.21; 1213.6.

The ethyl ester compounds of family Ih as defined above were prepared according to a similar process.

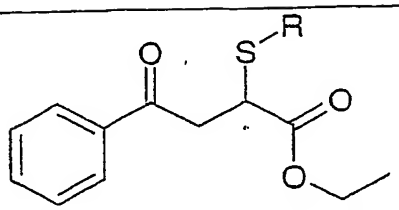
The compounds of family Ih are collated in Tables I 1-4 below. The purities were determined by HPLC/MS.

Compounds Ih 

R-SH	Number	Mass	Purity (%)	Yield (%)	m.p. (°C); (solvent*)
	1h	336.41	99	81.1	146 -149 (isopropyl ether)
	2h	286.35	99	67.6	132-135 (ethanol 85)
	3h	304.34	99	68.4	114-116 (isopropyl ether)
	4h	320.8	99	72.5	140-142 (ethanol 85)
	5h	300.38	99	66	132-134 (ethanol 95)
	6h	316.38	99	77.2	116-118 (ethanol 50)
	7h	292.4	99	6.8	117 (ethanol 50)
	8h	300.38	99	52.7	143-146 (ethanol 95)

* recrystallisation solvent

Table I-1

Compounds Ih 

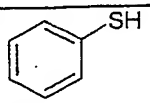
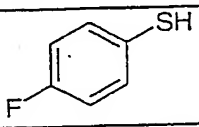
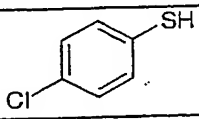
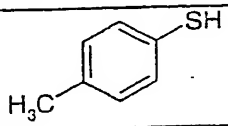
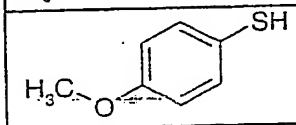
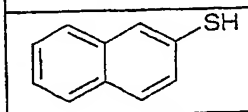
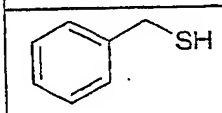
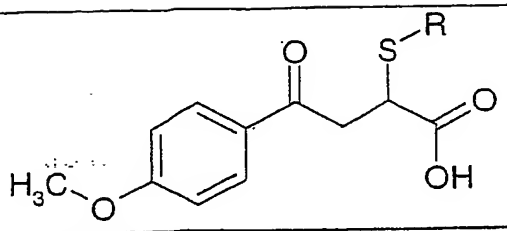
R-SH	Number	Mass	Purity (%)	Yield (%)	m.p. (°C); (solvent)
	9h	341.41	99	33	oil
	10h	332.4	97.4	24	oil
	11h	348.85	95.2	19.8	oil
	12h	328.43	94.4	24.2	oil
	13h	344.43	95.7	56.6	oil
	14h	364.47	94	9.6	oil
	15h	320.42	99	75.8	oil
	16h	328.43	99	41.2	oil

Table I-2

Compounds Ih 

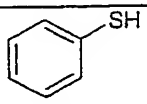
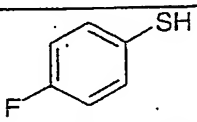
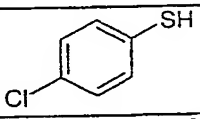
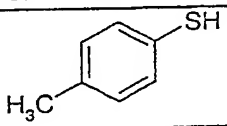
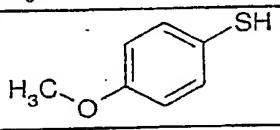
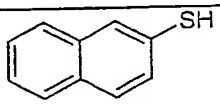
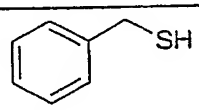
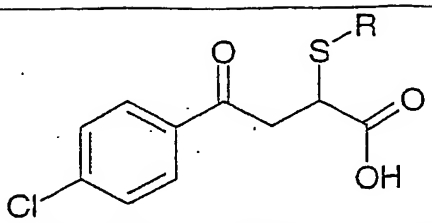
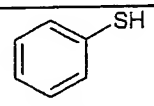
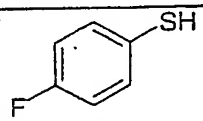
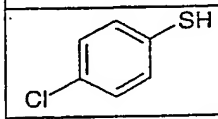
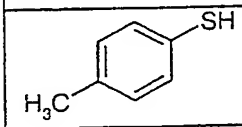
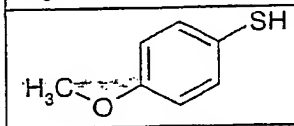
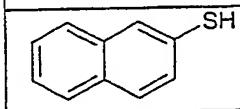
R-SH	Number	Mass	Purity (%)	Yield (%)	m.p. (°C); (solvent*)
	17h	316.38	99	70.4	121-125 (ethanol 50)
	18h	334.37	98.2	51.3	108-110 (ethanol 50)
	19h	350.82	99	68	120-121 (ethanol 50)
	20h	330.41	99	23.2	137-141 (ethanol 70)
	21h	346.4	99	68	137-140 (ethanol 70)
	22h	366.44	99	87.4	167-169 (ethanol 50)
	23h	322.43	96.7	30.4	120-122 (ethanol 50)
	24h	330.41	91.8	72.5	105-109 (ethanol 50)

Table I-3

Compounds Ih



R-SH	Number	Mass	Purity (%)	Yield (%)	m.p. (°C); (solvent*)
	25h	320.8	98.5	78.5	166-169 (ethanol 85)
	26h	338.79	98.6	81.2	140-141 (ethanol 85)
	27h	355.24	97.8	82.8	154-156 (ethanol 85)
	28h	334.82	99	62.9	151-153 (ethanol 85)
	29h	350.82	99	54.2	117-119 (ethanol 70)
	30h	370.86	96.6	82.7	141-145 (isopropyl ether)

* recrystallisation solvent

Table I-4

Study of the inhibitory activity on kynurenine 3-hydroxylase in rat liver

Experimental protocol

Rat livers are homogenised (1:8 weight/volume) in a buffer solution comprising: 0.25 M sucrose; 50 mM pH 7.4 Tris; 1 mM EDTA; and 1 mM DTT.

The homogenates are centrifuged for 10 minutes at 12 000 rpm. The pellets are resuspended in the buffer solution described above (1:2 weight/volume).

The kynurenine 3-hydroxylase inhibition is determined by incubating 10 µL of the homogenate with NADPH (2 mM), kynurenine (100 µM) and various concentrations of the test compounds in a final volume of 100 µL at 37°C for 5 minutes.

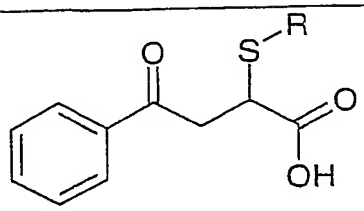
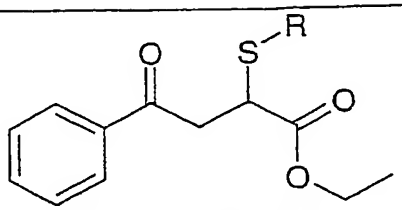
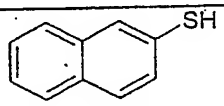
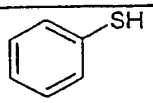
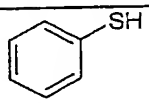
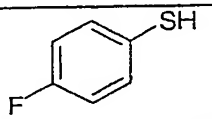
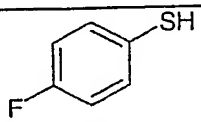
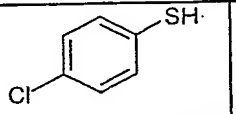
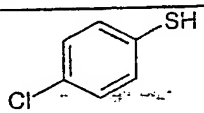
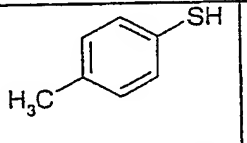
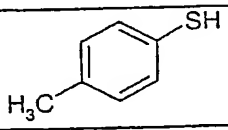
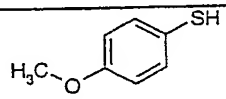
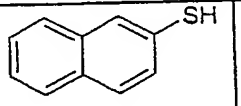
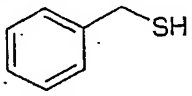
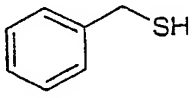
The compounds are tested at concentrations of between 1 µM and 300 µM. 3,4-Dimethoxy-N-[4-(3-nitrophenyl)thiazol-2-yl]benzenesulfonamide is a compound from the company Hoffmann-LaRoche (Basle, see *J. Med. Chem.*, **40** (1997), 4738). 30H-Kynurenine was tested according to the protocol described by Carpendo et *al.* (*Neuroscience*, **61** (1994), 237-244).

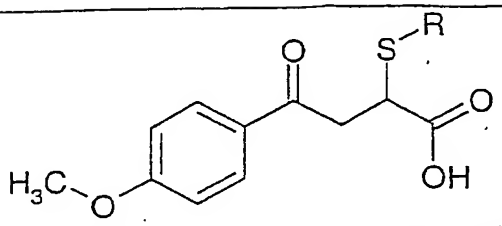
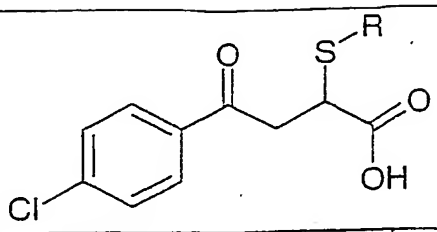
Results:

Each of the experiments is repeated once and the IC_{50} values (in µmol/L) are calculated and given in the form of a mean of these two experiments.

By way of example, (*R*)-2-benzyl-4-(4-fluorophenyl)-4-oxobutanoic acid (compound i) has an IC_{50} value of 1 ± 0.2 µmol/L, whereas 3,4-dimethoxy-N-[4-(3-nitrophenyl)thiazol-2-yl]benzenesulfonamide (compound k) has an IC_{50} value of 10 ± 2.1 µmol/L.

Results concerning representative examples of family Ih are given in Table II below, in which is indicated the measurement of the percentage of remaining kynurenine 3-hydroxylase activity relative to the control (100%).

					
R-SH	**Ih**	**Kynurenine 3-hydroxylase inhibition 10 µM % control**	**R-SH**	**Ih**	**Kynurenine 3-hydroxylase inhibition 10 µM % control**
	Ih-1	23.2		Ih-9	80.8
	Ih-2	70.4		Ih-10	66.7
	Ih-3	50.4		Ih-11	44.6
	Ih-4	34.8		Ih-12	63.3
	Ih-5	45.4		Ih-13	55.2
	Ih-7	81.3		Ih-14	30.0
	Ih-8	68.6		Ih-15	95.0
				Ih-16	84.4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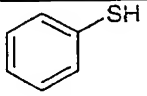
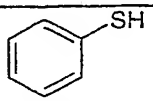
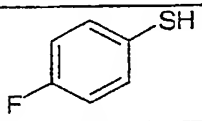
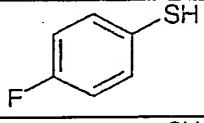
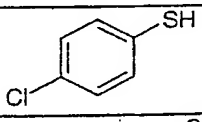
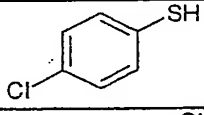
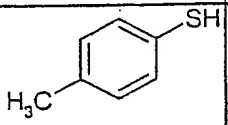
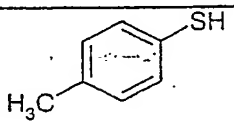
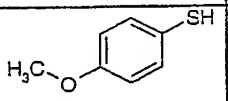
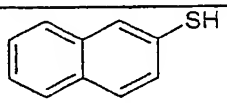
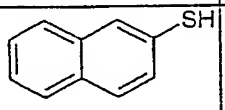
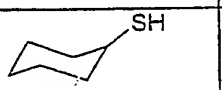
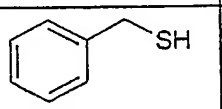
	Ih-17	16.0		Ih-25	67.6
	Ih-18	6.6		Ih-26	55.5
	Ih-19	4.1		Ih-27	34.9
	Ih-20	13.3		Ih-28	50.5
	Ih-21	17.4		Ih-30	24.3
	Ih-22	8.5			
	Ih-23	38.1			
	Ih-24	18.9			

Study of the antidiabetic activity in N0STZ rats

The antidiabetic activity of the compounds of the formulae (I) and (II) orally was determined on an experimental model of non-insulin-dependent diabetes, induced in rats with steptozotocin.

The model of non-insulin-dependent diabetes is obtained in the rats by means of a neonatal injection (on the day of birth) of steptozotocin.

The diabetic rats used are eight weeks old. The animals are housed, from the day of birth to the day of the experiment, in an animal house at a regulated temperature of 21 to 22°C and subjected to a fixed cycle of light (from 7 a.m. to 7 p.m.) and darkness (from 7 p.m. to 7 a.m.). Their food consisted of a maintenance diet, and water and food were given "ad libitum", with the exception of fasting two hours before the tests, during which period the food is removed (post-absorptive state).

The rats are treated orally for one (D1) or four (D4) days with the test product. Two hours after the final administration of the product and 30 minutes after anaesthetising the animals with pentobarbital sodium (Nembutal®), a 300 µL blood sample is taken from the end of the tail.

Among the compounds of the formula (I), the compounds of the family (Ih), especially the compounds of the subfamily (Ii), in particular compound Ih-1 defined previously (2-(2'-naphthylthio)-4-phenyl-4-oxobutanoic acid) and compound Ih-3 of the subfamily (Ij) (2-(4'-fluorophenylthio)-4-phenyl-4-oxobutanoic acid) were evaluated according to the experimental protocol described above.

The results presented below are expressed as a percentage change in the glycaemia on D1 and D4 (number of days of treatment) relative to D0 (before the treatment).

Compound	D1 (20 mg)	D1 (200 mg)	D4 (20 mg)	D4 (200 mg)
Ih-3	-3	7	-19	-12
Ih-1	7	10	-12	-21

These results show the efficacy of the compounds, especially of the formula (Ih), in reducing glycaemia in the diabetic animals.

This antidiabetic activity is correlated with an inhibitory effect of this family of molecules on kynurenine 3-hydroxylase.

Study of the effect on glucose production by the liver

Materials and method:

The hepatocytes are isolated from the liver of Wistar rats fasted for 24 hours, according to the method described in *Methods Cell Biol.*, **13** (1975), 29-83.

The following two methods were used:

1) The hepatocytes are cultured for 16 to 18 hours in DMEM medium in the presence of AMP cyclase/dexamethasone at respective concentrations of 5×10^{-5} M and 5×10^{-7} M, with preincubation of the products at the test doses. After washing in pH 7.4 PBS buffer, the cells are incubated for three hours at 37°C in a Krebs/AMPc/DEX buffer at the abovementioned concentrations. 0.1 µM insulin is used as reference substance. Two identical experiments are performed (Table III-1).

2) The hepatocytes are cultured for 16 to 18 hours in RPMI 1640 medium free of glucose but supplemented with 1% glutamine, 100 U/mL penicillin, 100 mg/mL streptomycin and 7×10^{-5} M hydrocortisone hemisuccinate.

After washing in pH 7.4 PBS buffer, the cells are incubated for two hours at 37°C in a Krebs buffer free of glucose and of insulin, containing lactate/pyruvate (10/1 mM) in the presence or absence of the test compounds. 10 µM MICA (5-methoxyindole-2-carboxylic acid) is used as reference substance. Two identical experiments are performed (Table III-2).

Quantification of the glucose is performed via a colorimetric method using glucose oxidase (*IL test™ Glucose, Monarch 181633-80*). The protein assay is performed on the rest of the incubation medium via the Lowry method (*BIO-RAD Dc protein assay, BIO-RAD 5000116*).

The results are expressed as nmoles of glucose produced per ng of proteins. The statistical test used is the t test.

Results:

It was thus demonstrated that tryptophan and kynurenine are powerful inhibitors of hepatic glucose production *in vitro*.

Effect of kynurenine 3-hydroxylase inhibitors

By way of example, compound Ih-1 (Table III 1-3) and (*R*)-2-benzyl-4-(4-fluorophenyl)-4-oxobutanoic acid (compound i) and (*R,S*)-2-benzyl-4-(3',4'-dichlorophenyl)-4-oxobutanoic acid (compound j) (Table IV), two kynurenine 3-hydroxylase inhibitors, were found to be powerful inhibitors of hepatic glucose production *in vitro*, as shown by the following results:

Products tested on primary hepatocytes
Hepatic Glucose Production
stimulated by AMPc / DEX

Products	Test Concentration	HGP % of control	Proteins % of control
Ih-1	1 μM	103	113
	10 μM	83	117
	100 μM	15	85

Table III-1

Products tested on primary hepatocytes
Hepatic Production Glucose
Basal Lact/Pyr 2 hours

Products	Test Concentration	HGP % of control	Proteins % of control
Ih-1	1 μM	110	94
	10 μM	127	101
	100 μM	75	96

Table III-2

Compound	*Concentration (μM)*	*Hepatic glucose production (mmol/mg of protein)*	*Inhibition (%)*
MICA	10		67**
Compound i	0	101 ± 6	-
	1	88 ± 7	13
	10	73 ± 4	28**
	100	39 ± 3	62**
Compound j	0	101 ± 6	-
	1	71 ± 3	30**
	10	50 ± 3	51**
	100	35 ± 1	65**
Compound k	0	587 ± 12	-
	10	605 ± 24	0
	100	460 ± 12	22
Kynurenine	0	101 ± 6	-
	1	99 ± 5	2
	10	97 ± 6	4
	100	66 ± 4	25**
	1000	22 ± 2	78**
Tryptophan	0	587 ± 12	-
	10	518 ± 8	12
	100	111 ± 5	81**

Table IV

Study of the effect on the secretion of the pancreatic hormones insulin and glucagon, in N0STZ diabetic rats

Materials and method:

The pancreas is taken from animals rendered diabetic by injection of streptozotocin on the day of birth (Portha et *al.*, *Diabetes, 23*: 889-895; (1974)) and anaesthetised with pentobarbital (Nembutal: 45 mg/kg; intraperitoneal route).

The isolation and perfusion of the pancreas were performed according to a modification (Assan et *al.*, *Nature, 239* (1972), 125-126) of the protocol described by Sussman et *al.* (*Diabetes, 15* (1966), 466-472).

The effect of the compounds or of the reference substances is tested for 35 minutes (from t = 20 minutes to t = 55 minutes) in Krebs buffer in the absence of glucose, and then for 30 minutes (from t = 55 minutes to t = 85 minutes) in the presence of 16.5 mM glucose.

The concentration of the hormones, insulin and glucagon, secreted into the medium is measured via a competitive radioimmunoassay using the kits: Insulin-CT Cis Bio-International, Schering and Glucagon –10904- Biochem immuno system, respectively.

The results are expressed as the mean ± SEM (standard error of mean) of several experiments. The statistical test used is the Scheffé test.

Results:

Effect of tryptophan and its metabolites on the secretion of insulin and glucagon in perfused isolated pancreases from N0 STZ diabetic rats

Figure 1 shows that tryptophan stimulates insulin secretion in a glucose-dependent manner in a diabetic rat pancreas. Similarly, Figure 2 shows that tryptophan stimulates glucagon secretion in a glucose-dependent manner in a diabetic rat pancreas.

Kynurenic acid, like tryptophan, stimulates the secretion of insulin (Figure 3) and of glucagon (Figure 4) in a glucose-dependent manner in a diabetic rat pancreas.

Figure 5 and Figure 6 show the secretion profile for insulin and glucagon, respectively, stimulated with kynurenine (at 10^{-4} M and 10^{-5} M) in a glucose-dependent manner in a diabetic rat pancreas. This stimulation is similar to that obtained with tryptophan and kynurenic acid.

Effect of kynurenine 3-hydroxylase inhibitors on the secretion of insulin and glucagon in perfused isolated pancreases from N0 STZ diabetic rats

The kynurenine 3-hydroxylase inhibitors show the same insulin and glucagon secretion profile as for tryptophan, kynurenine and kynurenic acid. This observation may be seen in Figures 7 and 8 (stimulation of insulin and of glucagon, respectively, with compound i) and in Figures 9 and 10 (stimulation of insulin and of glucagon, respectively, with compound k).

STUDY OF THE ACTIVITY ON ISOLATED RAT ISLETS

Effect of the chemical compounds on insulin secretion as a function of the glucose concentration, *in* vitro, in isolated islets of Langerhans in static incubation:

The islets of Langerhans obtained by digestion of exocrine pancreatic tissue with collagenase, and then purified on Ficoll gradient, are incubated for 90 minutes in the presence of two concentrations of glucose, (2.8 mM or 8 mM), in the presence or absence of the chemical compound. The insulin secretion is assayed by RIA in the incubation medium.

The potential of the various chemical compounds to stimulate insulin secretion is estimated by calculating the stimulation factor*.

A compound stimulates the secretion of insulin if this factor is greater than or equal to 130% for a given dose of insulin.

*NB : stimulation factor = $\frac{(G + Product)*100}{G}$

where :

- G= secretion of insulin (pmol/min. islet) in the presence of glucose alone

- G+Product = secretion of insulin (pmol/min. islet)
  in the presence of the same concentration of glucose and of the test chemical compound.

Figure 11 shows the insulin secretion for compounds Ih-18 and (i) at 10^{-5} M at glucose concentrations of 2.8 mM and 8 mM.

Study of the effect on the increase in the mass of beta cells

Culturing of rat foetal pancreases

Experimental protocol

Embryonic pancreases are collected on day 12.5 of gestation from gestating females of the Wistar strain, which have received an overdose of sodium pentobarbital. The embryos are extracted from the uterus and placed in phosphate-buffered saline (PBS). The dorsal pancreatic bud is dissected under stereomicroscopy. The separation of the mesenchyme, which inhibits the development of the endocrine pancreas, is performed via an enzymatic reaction with 0.05% concentrated collagenase A in the synthetic culture medium RPMI 1640.

The pancreatic epithelia thus isolated are inserted into a collagen gel, which allows three-dimensional culturing to be performed. The pancreases are cultured in the RPMI 1640 culture medium supplemented with 10% foetal calf serum and 5.5 mM glucose and in the absence (control) or in the presence of the test compounds. The cultures are maintained at 37°C in the presence of 5% CO_2 for seven days. The culture medium is renewed every day.

At the end of the seven days of culturing, the pancreases are isolated from the collagen gels and dissociated into individual cells by means of a trypsin digestion (0.05% trypsin-EDTA) for three minutes at 37°C. The enzymatic reaction is quenched by adding RPMI 1640 medium containing 20% foetal calf serum. The cells are washed with the same medium and then fixed to glass slides using a cytocentrifuge for five minutes at 125xg. The cells are then treated with 4% paraformaldehyde, and then incubated overnight at 4°C with guinea pig anti-

insulin antibody (1:1500 dilution). After washing several times with PBS, they are incubated with FITC-coupled rabbit anti-guinea pig IgG (dilution 1:100) for 75 minutes at room temperature. The cells are finally mounted in a medium that protects the fluorescence and that contains DAPI for labelling the cell nuclei. On each slide, a minimum of 300 nuclei and the amount of cells expressing insulin are counted. The calculation of the amount of beta cells represents the proportion of cells expressing insulin to the total number of nuclei counted. An experiment is performed with a minimum of four pancreases per group and each experiment is repeated three times.

Figures 12, 13, 14 and 15 represent the amount of beta cells expressing insulin in the cultured rat foetal pancreatic buds over seven days, with or without test compound. The increase in the number of beta cells is mainly due to stimulation of the neogenesis of these cells from the stems cells.